

=> fil reg

FILE 'REGISTRY' ENTERED AT 07:29:48 ON 13 APR 2004
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STRUCTURE FILE UPDATES: 11 APR 2004 HIGHEST RN 673857-36-8
DICTIONARY FILE UPDATES: 11 APR 2004 HIGHEST RN 673857-36-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d sqide can l58

L58 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 107335-26-2 REGISTRY
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide
deriv.
OTHER NAMES:
CN SDZ 211-810
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 11
NTE cyclic
modified (modifications unspecified)

type	-----	location	-----	description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

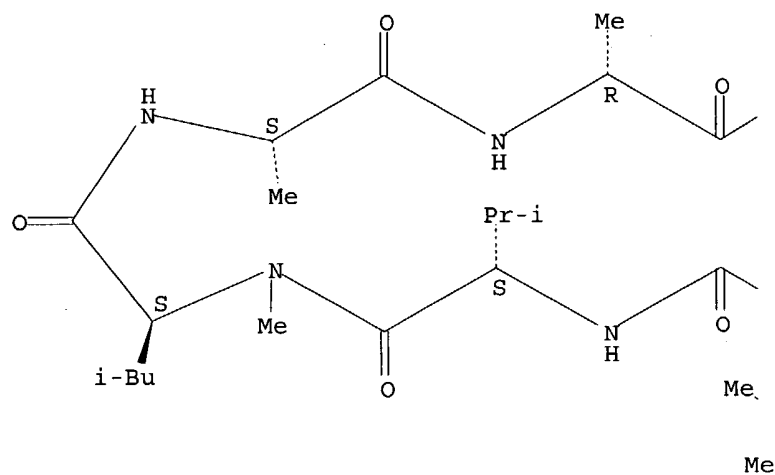
SEQ 1 XXXLVLAALL V

RELATED SEQUENCES AVAILABLE WITH SEQLINK

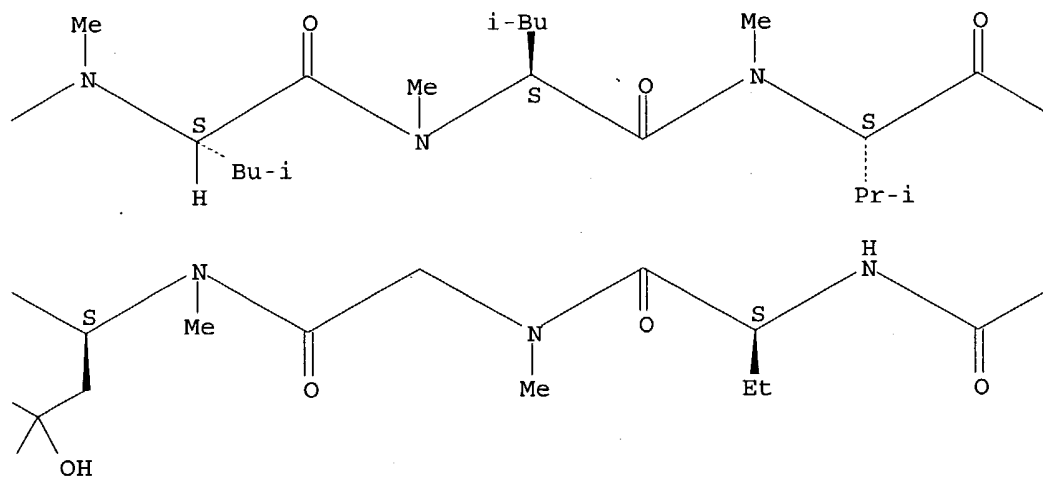
DR 215435-99-7
MF C62 H111 N11 O13
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

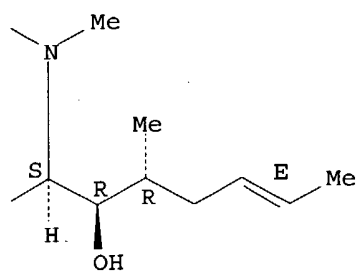
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26 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:389028
 REFERENCE 2: 137:362480
 REFERENCE 3: 137:345609
 REFERENCE 4: 136:337615
 REFERENCE 5: 136:252244
 REFERENCE 6: 134:371585
 REFERENCE 7: 132:175375
 REFERENCE 8: 132:36039
 REFERENCE 9: 132:18781
 REFERENCE 10: 131:59141

=> d his

(FILE 'HOME' ENTERED AT 06:39:58 ON 13 APR 2004)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 06:40:11 ON 13 APR 2004

L1 5 S GAMMA () (OH OR HYDROX?) () N () METHYL (1W) LEUC? (L) CYCLOS
 L2 4 S GAMMA () (OH OR HYDROX?) () N () METHYL (1W) LEUC? (L) ?CYCLO
 L3 5 S L1,L2
 L4 1 S US20020165133/PN OR KR2001-7263/AP,PRN
 E KIM S/AU
 L5 706 S E3,E28
 E KIM SANG/AU
 L6 7 S E3
 E KIM SANG N/AU
 L7 20 S E3,E9
 E KIM SANGN/AU
 E AHN H/AU
 L8 76 S E3,E6
 E AHN HO/AU
 L9 28 S E5
 E LEE C/AU
 L10 413 S E3
 E LEE C W/AU
 L11 232 S E3-E7
 E LEE CHANG/AU
 L12 12 S E3
 E LEE CHANG W/AU
 L13 180 S E3,E9
 L14 13 S E65
 E KIM J/AU
 L15 1872 S E3,E14-E17
 E KIM JUNG/AU
 L16 84 S E3,E42,E57
 E KIM JUNGH/AU
 E KIM J/AU
 L17 324 S E21
 E KIM JONG/AU

L18 23 S E3
 E KIM JONG I/AU
 L19 67 S E3-E5
 E KIM JONGI/AU
 L20 2 S E4
 E LEE H/AU
 L21 513 S E3
 E LEE H S/AU
 L22 557 S E3,E4
 E LEE HEON/AU
 L23 48 S E3,E18
 E LEE HEONS/AU
 E LEE M/AU
 L24 723 S E3,E20-E21
 E LEE MIN/AU
 L25 12 S E3
 E LEE MIN H/AU
 L26 82 S E3,E8
 E LEE MINH/AU
 L27 12 S E7
 E CHO H/AU
 L28 275 S E3,E23
 E CHO HO/AU
 L29 30 S E3,E11-E13
 E CHO HOS/AU
 E KIM S/AU
 E KIM S J/AU
 L30 468 S E3
 E KIM SEUNG/AU
 L31 56 S E3,E64,E65
 E KIM SEUNG J/AU
 L32 46 S E8
 E KIM SEUNGJ/AU
 L33 10 S E5
 E PARK H/AU
 L34 686 S E3
 L35 222 S E20
 E PARK HONG/AU
 L36 105 S E49,E50
 E PARK HONGS/AU
 L37 2 S E6,E7
 E LG/PA,CS
 L38 4081 S E3,E4
 L39 5 S L3 AND L4-L38
 SEL RN

FILE 'REGISTRY' ENTERED AT 06:50:51 ON 13 APR 2004

L40 53 S E1-E53
 L41 31 S L40 AND CYCLOSPORIN
 L42 22 S L40 NOT L41
 L43 4 S L42 AND SQL/FA
 L44 35 S L41,L43
 L45 18 S L40 NOT L44
 L46 23 S L44 AND LEUC?
 L47 12 S L44 NOT L46
 L48 20 S L46 AND N METHYL(1W)LEUC?
 L49 15 S L48 AND HYDROX?
 L50 8 S L49 AND 9
 L51 3 S L50 NOT (SERINE OR ALANINE OR THREONINE)
 L52 5 S L50 NOT L51
 L53 7 S L49 NOT L50
 L54 5 S L48 NOT L49
 L55 2 S L54 AND 9 DE

L56 1 S L55 NOT ACETATE
L57 1 S CYCLOSPORIN A/CN
SEL RN L51
L58 1 S 107335-26-2
E C62H111N11O13/MF
L59 37 S E3
L60 35 S L59 AND 11/SQL
L61 4 S L60 AND 9
L62 0 S 107335-26-2/CRN

FILE 'HCAOLD' ENTERED AT 07:17:18 ON 13 APR 2004

L63 0 S L58

FILE 'USPATFULL, USPAT2' ENTERED AT 07:17:22 ON 13 APR 2004

L64 9 S L58
L65 8 S L1 OR L2
L66 16 S L64, L65

FILE 'HCAPLUS' ENTERED AT 07:18:24 ON 13 APR 2004

L67 26 S L58
L68 2 S SDZ21180 OR SDZ() (211810 OR 211 810)
L69 29 S L3, L67, L68
L70 6 S L69 AND L5-L38
L71 6 S L4, L39, L70

FILE 'REGISTRY' ENTERED AT 07:20:04 ON 13 APR 2004

L72 2 S L51 NOT L58

FILE 'HCAPLUS' ENTERED AT 07:20:42 ON 13 APR 2004

L73 114 S L72
L74 24 S L69 AND (PD<=20010214 OR PRD<=20010214 OR AD<=20010214)
L75 3 S L69 NOT L71, L74
L76 26 S L71, L74
L77 6 S L76 AND HAIR
L78 5 S L76 AND (BALD OR BALDNESS OR BALDING OR ALOPEC?)
L79 6 S L77, L78
E HAIR/CT
L80 31230 S E3-E90
E E3+ALL
L81 30764 S E6, E5+NT
E E13+ALL
L82 2313 S E6+NT
E E9+ALL
E E14+ALL
L83 736 S E6
E E8+ALL
E E15+ALL
L84 20122 S E2+NT
E E8+ALL
E E16+ALL
L85 228 S E5, E4+NT
E E7+ALL
E E17+ALL
L86 428 S E4, E3+NT
E E11+ALL
E E18+ALL
L87 860 S E4+NT
E E6+ALL
E E19+ALL
L88 2201 S E3, E2+NT
L89 6 S L76 AND L80-L88
L90 6 S L79, L89
L91 9 S L58 (L) (COS OR THU) /RL

L92 7 S L91 AND L76
 L93 5 S L92 NOT L90
 L94 6 S L76 AND COSMETIC#/SC,SX,CW
 L95 6 S L90,L94
 L96 20 S L76 NOT L95
 L97 6 S L95 AND L1-L39,L67-L71,L74-L96

FILE 'REGISTRY' ENTERED AT 07:29:48 ON 13 APR 2004

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 07:30:03 ON 13 APR 2004

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FILE COVERS 1907 - 13 Apr 2004 VOL 140 ISS 16

FILE LAST UPDATED: 12 Apr 2004 (20040412/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l97 all hitstr tot

L97 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:888509 HCAPLUS

DN 137:389003

ED Entered STN: 22 Nov 2002

TI The use of nonimmunosuppressive [γ -hydroxy-N-methyl-L-leucine⁴] cyclosporin derivatives for treating hair loss

IN Kim, Sang-Nyun; Ahn, Ho-Jeong; Lee, Chang-Woo; Lee, Min-Ho; Kim, Jung-Hun; Kim, Jong-Il; Kim, Seung-Jin; Cho, Ho-Song; Lee, Heon-Sik; Kim, Hyung-Jin

PA LG Household & Health Care Ltd., S. Korea

SO PCT Int. Appl., 51 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K007-06

CC 62-3 (Essential Oils and Cosmetics)

Section cross-reference(s): 16, 34

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002092033	A1	20021121	WO 2002-KR880	20020511

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,

UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1392224 A1 20040303 EP 2002-730937 20020511
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 PRAI KR 2001-27022 A 20010517
 WO 2002-KR880 W 20020511
 OS MARPAT 137:389003
 AB The present invention discloses a hair growth promoting agent
 comprising a cyclosporin derivative having an excellent hair
 growth stimulating ability with little immunosuppressive effect as an
 active ingredient. The derivs. of the invention were prepared by
 derivatization of cyclosporins at the amino acid residue 4,
 N-methyl-L-leucine, and hair growth promoting effects were
 examined. Such a hair growth promoting agent, comprising a
 cyclosporin derivative as an active ingredient, exhibits an excellent
 hair growth effect, while it shows very weak immunosuppressive
 activity, compared to unmodified cyclosporin A. E.g.,
 [N-methyl-D-alanine3][γ -hydroxy-N-
 methyl-L-leucine4]-cyclosporin A was
 prep including a step involving bacterial strain Sebekia benihana KCTC
 9173 culture and this derivative was formulated in a hair tonic.
 ST hair loss treatment cyclosporin deriv prepn
 IT Hair preparations
 (growth stimulants; nonimmunosuppressive [
 γ -hydroxy-N-methyl-L-
 leucine4] cyclosporin derivs. for treating
 hair loss)
 IT Alopecia
 Shampoos
 (nonimmunosuppressive [γ -hydroxy-N-
 methyl-L-leucine4] cyclosporin derivs. for
 treating hair loss)
 IT 89288-32-4P 475476-16-5P 475476-17-6P 475476-18-7P
 RL: BMF (Bioindustrial manufacture); COS (Cosmetic use); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (nonimmunosuppressive [γ -hydroxy-N-
 methyl-L-leucine4] cyclosporin derivs. for
 treating hair loss)
 IT 59865-13-3, Cyclosporin A
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (nonimmunosuppressive [γ -hydroxy-N-
 methyl-L-leucine4] cyclosporin derivs. for
 treating hair loss)
 IT 83602-41-9P 108466-41-7P 122958-60-5P 139050-39-8P 159391-83-0P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (nonimmunosuppressive [γ -hydroxy-N-
 methyl-L-leucine4] cyclosporin derivs. for
 treating hair loss)

RE.CNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Jacobs, J; International Journal of Dermatology 1993, V32(10), P758 MEDLINE
- (2) Maurer, M; Hair growth modulation by topical immunophilin ligands: Induction of anagen, inhibition of massive catagen development and relative protection from chemotherapy-induced alopecia 1997, V150(4), P1433 HCAPLUS
- (3) Novatis Ag; US 5807820 A 1998 HCAPLUS
- (4) Sandoz Ltd; US 5284826 A 1994 HCAPLUS
- (5) Yamamoto, S; Hair growth stimulating effects of cyclosporin A and FK506, potent immunosuppressants 1994, V7(suppl), PS47

L97 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2002:888507 HCAPLUS
 DN 137:389028
 ED Entered STN: 22 Nov 2002
 TI Topical compositions containing nonimmunosuppressive cyclosporin derivatives for treating hair loss
 IN Kim, Sang-Nyun; Ahn, Ho-Jeong; Lee, Chang-Woo
 ; Lee, Min-Ho; Kim, Jung-Hun; Kim, Jong-Il;
 Kim, Seung-Jin; Cho, Ho-Song; Lee, Heon-Sik;
 Kim, Hyung-Jin; Kim, Jin-Chul; Park, Seung-Kyu
 PA LG Household & Health Care Ltd., S. Korea
 SO PCT Int. Appl., 65 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K007-06
 CC 62-4 (Essential Oils and Cosmetics)
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002092031	A1	20021121	WO 2002-KR861	20020509
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1389086	A1	20040218	EP 2002-733514	20020509
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	KR 2001-26503	A	20010515		
	WO 2002-KR861	W	20020509		

OS MARPAT 137:389028
 AB The present invention discloses a topical scalp and transdermal preparation with excellent penetration to the skin and follicle, containing a [**gamma.-hydroxy-N-methyl-L-leucine4**] cyclosporin derivative which is a non-immunosuppressive component with hair growth stimulating ability. The topical scalp and transdermal preparation is prepared by incorporating the cyclosporin derivative into a liposome, microcapsule, micro-sphere, composite particle or emulsion, capable of being employed as a hair growth stimulating agent and applied for the prevention of hair loss.
 ST topical cosmetic nonimmunosuppressive cyclosporin deriv hair loss
 IT Cosmetics
 (emulsions; topical compns. containing nonimmunosuppressive cyclosporin derivs. for treating hair loss)
 IT Hair preparations
 (growth stimulants; topical compns. containing nonimmunosuppressive cyclosporin derivs. for treating hair loss)
 IT Alopecia
 Microcapsules
 Microspheres
 Particles
 Shampoos
 (topical compns. containing nonimmunosuppressive cyclosporin derivs. for treating hair loss)

IT 59787-61-0D, Cyclosporin C, derivs. 59865-13-3D, Cyclosporin A, derivs.
 79217-60-0, Cyclosporin 89288-32-4 107335-26-2 475476-17-6
 475476-18-7 475562-60-8 475562-61-9 475562-62-0
 RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
 (topical compns. containing nonimmunosuppressive cyclosporin derivs. for
 treating hair loss)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Jacobs, J; International Journal of Dermatology 1993, V32(10), P758 MEDLINE
- (2) Maurer, M; Hair growth modulation by topical immunophilin ligands: Induction of anagen, inhibition of massive catagen development and relative protection from chemotherapy-induced alopecia 1997, V150(4), P1433 HCAPLUS
- (3) Novatis Ag; US 5807820 A 1998 HCAPLUS
- (4) Sandoz Ltd; US 5284826 A 1994 HCAPLUS
- (5) Yamamoto, S; Hair growth stimulating effects of cyclosporin A and FK506, potent immunosuppressants 1994, V7(suppl), PS47

IT 107335-26-2

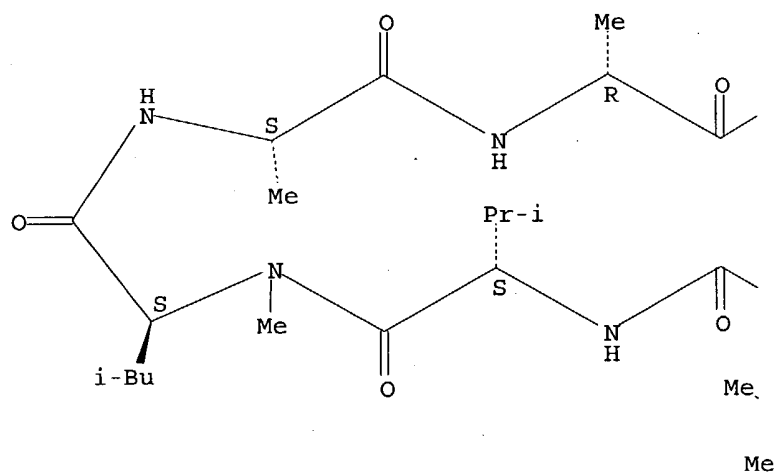
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
 (topical compns. containing nonimmunosuppressive cyclosporin derivs. for
 treating hair loss)

RN 107335-26-2 HCAPLUS

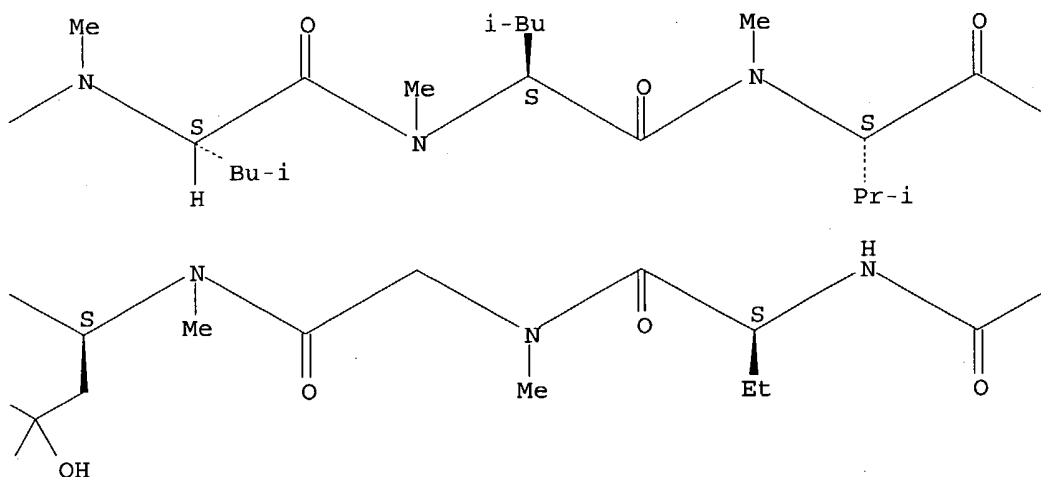
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

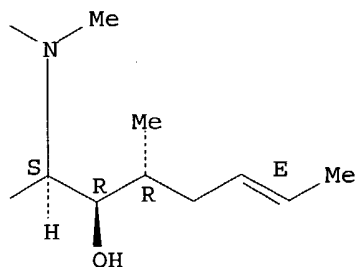
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PAGE 1-C



L97 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2002:637493 HCAPLUS
 DN 137:179921
 ED Entered STN: 23 Aug 2002
 TI Use of [γ -hydroxy-N-methyl
 -L-leucine9]cyclosporin A for hair
 growth
 IN Kim, Sang-nyun; Ahn, Ho-jeong; Lee, Chang-woo
 ; Kim, Jung-hun; Kim, Jong-il; Lee, Heon-sik
 ; Lee, Min-ho; Cho, Ho-song; Kim, Seung-jin;
 Park, Hong-soon
 PA Lg Household & Health Care Ltd., S. Korea
 SO PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K007-06
 CC 1-12 (Pharmacology)
 Section cross-reference(s): 16, 62, 63
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2002064106 A1 20020822 WO 2002-KR141 20020131 <--
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 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1361850 A1 20031119 EP 2002-712478 20020131 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 US 2002165133 A1 20021107 US 2002-73021 20020212 <--
 PRAI KR 2001-7263 A 20010214 <--
 WO 2002-KR141 W 20020131

AB The present invention discloses a **hair** growth promoter comprising [γ -**hydroxy-N-methyl-L-leucine9**] **cyclosporin A**, in which a hydroxy group is added to a γ carbon of N-methyl-L-leucine at Number 9 position in **cyclosporin A** by metabolic action of a microorganism, as an active ingredient. This **cyclosporin A** metabolite was prepared by fermentation with *Pseudonocardia autotrophica*. The metabolite showed **hair** regrowth effect comparable to that of **cyclosporin A** and had lower immunosuppressive effect than **cyclosporin A**. **Hair** revitalizing tonic, cream, shampoo, and conditioner formulations are given.

ST hydroxymethylleucine cyclosporin A **hair** growth promoter;
 cyclosporin A metabolite **hair** prepn growth stimulant

IT Alcohols, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (C16-18; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (conditioners; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (creams; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (emulsions; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (gels; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (growth stimulants; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (liqs.; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

IT **Hair preparations**
 (pastes; use of [γ -**hydroxy-N-Me-L-leucine9**]cyclosporin A for **hair** growth)

- IT Immunosuppression
(reduction of side effect of; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
(sprays; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Drug delivery systems
(topical; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Fermentation
Microsome
Perfumes
Pseudonocardia autotrophica
Shampoos
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Paraffin oils
Petrolatum
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 59865-13-3, Cyclosporin A
RL: BCP (Biochemical process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 89270-25-7P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 89270-23-5P, Cyclosporin A metabolite 21
89270-28-0P, Cyclosporin A metabolite 17
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 156047-45-9
RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 13139-15-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 56-81-5, Glycerin, biological studies 57-55-6, Propylene glycol, biological studies 58-95-7, Tocopherol acetate 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 94-13-3, Propylparaben 99-76-3 111-02-4, Squalene 122-19-0, Stearyldimethyl benzylammonium chloride 544-31-0 2216-51-5 9004-82-4

9005-64-5, Tween 20 25265-71-8, Dipropyleneglycol 25322-68-3,
Polyethyleneglycol 31566-31-1, Glycerine-monostearate 32128-65-7,
Polyoxyethylene octyldodecylether

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(use of [γ -hydroxy-N-Me
-L-leucine9]cyclosporin A for
hair growth)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Novartis Ag; US 5807820 A 1998 HCAPLUS

(2) Sandoz Ltd; EP 414632 A 1989 HCAPLUS

L97 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:205027 HCAPLUS

DN 136:252244

ED Entered STN: 19 Mar 2002

TI Hair growth stimulants containing nonimmunosuppressive
[γ -hydroxymethylleucine4]cyclosporin A

IN Kim, Sang Nyun; Ahn, Ho Jeong; Kim, Myung Kee;
Kim, Jong Il; Kim, Jung Hun; Lee, Chang Woo;
Lee, Min Ho; Kim, Chang Deok; Cho, Ho Song; Kim, Hyun
Sik; Jung, Min Hwan; Kim, Seung Jin

PA LG Chemical Co., Ltd., S. Korea

SO Jpn. Kokai Tokkyo Koho, 14 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

IC ICM A61K038-00

ICS A61K007-06; A61K007-075; A61K007-08; A61P017-14

CC 62-3 (Essential Oils and Cosmetics)

Section cross-reference(s): 16

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2002080394	A2	20020319	JP 2000-347204	20001114 <--
PRAI	KR 1999-51646	A	19991119	<--	
	KR 2000-14837	A	20000323	<--	
	JP 2000-207588	A	20000707	<--	
AB	The stimulants, useful for treatment of alopecia, contain [γ -hydroxymethylleucine4]cyclosporin A (I) as active ingredients. Thus, I (preparation given) stimulated hair growth in mice as strongly as cyclosporin A, but the immunosuppressive activity of I was >100 times less potent than the control. A hair tonic, cream, shampoo, and conditioner containing I were formulated.				
ST	nonimmunosuppressive hydroxymethylleucine cyclosporin A hair growth; alopecia treatment nonimmunosuppressive hydroxymethylleucine cyclosporin A				
IT	Hair preparations (conditioners; hair growth stimulants containing nonimmunosuppressive [γ - hydroxymethylleucine4]cyclosporin A)				
IT	Hair preparations (creams; hair growth stimulants containing nonimmunosuppressive [γ -hydroxymethylleucine4]cyclosporin A)				
IT	Hair preparations (emulsions; hair growth stimulants containing nonimmunosuppressive [γ - hydroxymethylleucine4]cyclosporin A)				
IT	Hair preparations (gels; hair growth stimulants containing nonimmunosuppressive [γ -hydroxymethylleucine4]cyclosporin A)				

IT **Hair preparations**
 (growth stimulants; hair growth
 stimulants containing nonimmunosuppressive [γ -
 hydroxymethylleucine4]cyclosporin A)

IT **Shampoos**
 (hair growth stimulants containing nonimmunosuppressive
 [γ -hydroxymethylleucine4]cyclosporin A)

IT **Hair preparations**
 (pastes or liqs.; hair growth
 stimulants containing nonimmunosuppressive [γ -
 hydroxymethylleucine4]cyclosporin A)

IT **Hair preparations**
 (sprays; hair growth stimulants
 containing nonimmunosuppressive [γ -hydroxymethylleucine4]cyclosporin
 A)

IT **Alopecia**
 (treatment of; hair growth stimulants containing
 nonimmunosuppressive [γ -hydroxymethylleucine4]cyclosporin A)

IT 59865-13-3, Cyclosporin A
 RL: BCP (Biochemical process); RCT (Reactant); BIOL (Biological study);
 PROC (Process); RACT (Reactant or reagent)
 (hair growth stimulants containing nonimmunosuppressive
 [γ -hydroxymethylleucine4]cyclosporin A)

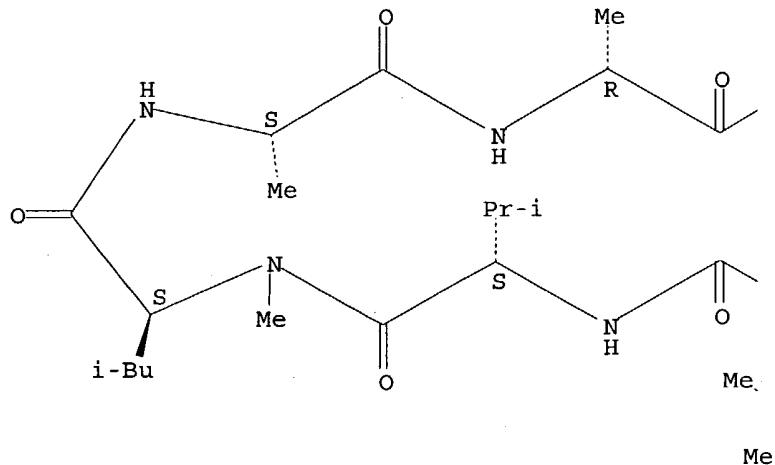
IT 107335-26-2P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 COS (Cosmetic use); BIOL (Biological study); PREP (Preparation);
 USES (Uses)
 (hair growth stimulants containing nonimmunosuppressive
 [γ -hydroxymethylleucine4]cyclosporin A)

IT 107335-26-2P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 COS (Cosmetic use); BIOL (Biological study); PREP (Preparation);
 USES (Uses)
 (hair growth stimulants containing nonimmunosuppressive
 [γ -hydroxymethylleucine4]cyclosporin A)

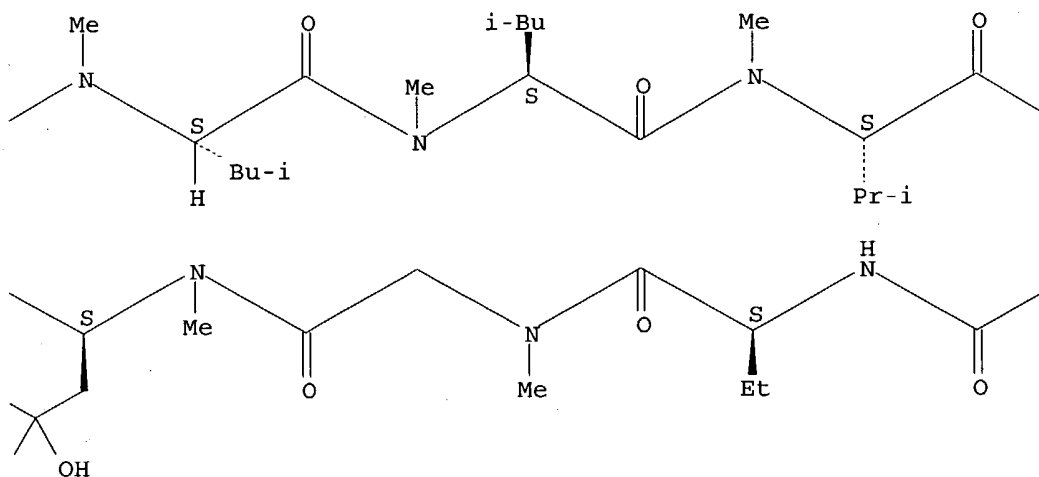
RN 107335-26-2 HCAPLUS
 CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

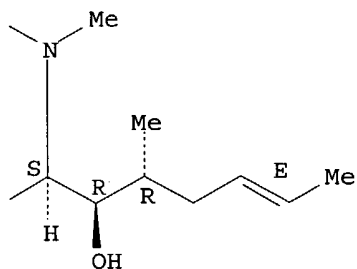
PAGE 1-A



PAGE 1-B



PAGE 1-C



L97 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:380358 HCAPLUS
 DN 134:371586
 ED Entered STN: 27 May 2001
 TI Nonimmunosuppressive cyclosporin derivatives for hair growth
 IN Kim, Sang Nyun; Ahn, Ho Jeong; Kim, Jong Il;
 Kim, Jung Hun; Lee, Min Ho; Kim, Chang Deok; Cho,
 Ho Song
 PA LG Chemical Co., Ltd., S. Korea
 SO PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K007-06
 CC 62-3 (Essential Oils and Cosmetics)
 Section cross-reference(s): 1, 34

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001035914	A1	20010525	WO 2000-KR1301	20001114 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,				

HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU,
 LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
 SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1233738 A1 20020828 EP 2000-976425 20001114 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2003514000 T2 20030415 JP 2001-537707 20001114 <--

PRAI KR 1999-51648 A 19991119 <--

WO 2000-KR1301 W 20001114 <--

AB The present invention relates to agents for treating alopecia and stimulating hair growth comprising an active ingredient of nonimmunosuppressive [γ -hydroxy-N-methyl-L-leucine4]cyclosporin B, C, D, or G having excellent hair growth-promoting effects, wherein the hydroxyl group is added to the γ -carbon position of Number 4 N-methyl-L-leucine of cyclosporin B, C, D, G by the microorganism. Thus, a hair revitalization tonic was prepared from EtOH 40.0, the above cyclosporin C deriv 0.1, tocopherol derivative 0.1, salicylic acid 0.3, l-menthol 0.3, and Tween-20 0.5%, perfume and dye qs, and water balance. The efficiency of the above tonic was comparable to that containing cyclosporin A.

ST nonimmunosuppressive cyclosporin deriv hair growth stimulant

IT Hair preparations

(conditioners; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Hair preparations

(creams; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Hair preparations

(gels; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Hair preparations

(growth stimulants; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Alopecia

(inhibitors; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Shampoos

(nonimmunosuppressive cyclosporin derivs. for hair growth)

IT Hair preparations

(sprays; nonimmunosuppressive cyclosporin derivs. for hair growth)

IT 59787-61-0P, Cyclosporin C 63775-95-1P, Cyclosporin B 63775-96-2P, Cyclosporin D 74436-00-3P, Cyclosporin G

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)

(nonimmunosuppressive cyclosporin derivs. for hair growth)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Maurer; Am J Pathol 1997, V150(4), P1433 HCAPLUS

(2) Yamamoto; J Dermatol Sci 1994, V7(Suppl), PS47

L97 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:380357 HCAPLUS

DN 134:371585

ED Entered STN: 27 May 2001

TI Nonimmunosuppressive cyclosporin A derivative for hair growth

IN Kim, Sang Nyun; Ahn, Ho Jeong; Kim, Myung Kee;
 Kim, Jong Il; Kim, Jung Hun; Lee, Chang Woo;
 Lee, Min Ho; Kim, Chang Deok; Cho, Ho Song; Kim, Hyun
 Sik; Jung, Min Hwan; Kim, Seung Jin
 PA Lg Chemical Co., Ltd., S. Korea
 SO PCT Int. Appl., 46 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC A61K007-06
 CC 62-3 (Essential Oils and Cosmetics)
 Section cross-reference(s): 1, 16, 34

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001035913	A1	20010525	WO 2000-KR1281	20001109 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6521595	B1	20030218	US 2000-580694	20000530 <--
	EP 1229889	A1	20020814	EP 2000-978090	20001109 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2000014635	A	20021001	BR 2000-14635	20001109 <--
	AU 760013	B2	20030508	AU 2001-15583	20001109 <--
PRAI	KR 1999-51646	A	19991119 <--		
	KR 2000-14837	A	20000323 <--		
	WO 2000-KR1281	W	20001109 <--		
AB	The present invention relates to agents for treating alopecia and stimulating hair growth comprising an active ingredient of nonimmunosuppressive [γ -hydroxy-N-methyl-L-leucine4]cyclosporin A (I) having superior hair growth-promoting effect, wherein the hydroxyl group is added to the γ carbon position of No.4 N-methyl-L-leucine of cyclosporin A by the microorganism. Thus, a hair tonic was prepared from EtOH 40.0, I 0.1, tocopherolacetic acid 0.1, salicylic acid 0.3, L-menthol 0.3, Tween-20 0.5, perfume and dye qs and water to 100%. I was obtained from Sebekia benihana culture. I not only had much lower degree of immunosuppression but also maintained superior hair growth effects to the nontransformed cyclosporin A.				
ST	nonimmunosuppressive cyclosporin A deriv hair growth stimulant				
IT	Hair preparations (conditioners; nonimmunosuppressive cyclosporin A derivative for hair growth)				
IT	Hair preparations (creams; nonimmunosuppressive cyclosporin A derivative for hair growth)				
IT	Hair preparations (emulsions; nonimmunosuppressive cyclosporin A derivative for hair growth)				
IT	Hair preparations (gels; nonimmunosuppressive cyclosporin A derivative for hair growth)				
IT	Hair preparations (growth stimulants; nonimmunosuppressive cyclosporin A derivative for hair growth)				
IT	Alopecia				

(inhibitors; nonimmunosuppressive cyclosporin A derivative for hair growth)

IT Sebekia benihana
Shampoos
(nonimmunosuppressive cyclosporin A derivative for hair growth)

IT Hair preparations
(sprays; nonimmunosuppressive cyclosporin A derivative for hair growth)

IT 107335-26-2P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nonimmunosuppressive cyclosporin A derivative for hair growth)

IT 83602-41-9P, O-AcetylCyclosporin A 89270-23-5P 111722-72-6P
143205-42-9P 156047-28-8P 156467-80-0P 157774-31-7P 340711-98-0P
340711-99-1P 340712-00-7P 340712-01-8P 340712-02-9P 340712-03-0P
340712-04-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nonimmunosuppressive cyclosporin A derivative for hair growth)

IT 59865-13-3, Cyclosporin A
RL: RCT (Reactant); RACT (Reactant or reagent)
(nonimmunosuppressive cyclosporin A derivative for hair growth)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

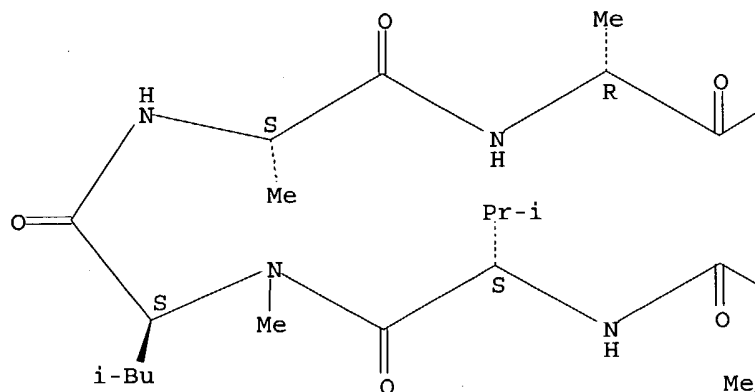
RE
(1) Maurer; Am J Pathol, American Society for Investigative Pathology 1997, V150(4), P1433 HCAPLUS
(2) Yamamoto; J Dermatol Sci 1994, V7(Suppl), PS47

IT 107335-26-2P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nonimmunosuppressive cyclosporin A derivative for hair growth)

RN 107335-26-2 HCAPLUS
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

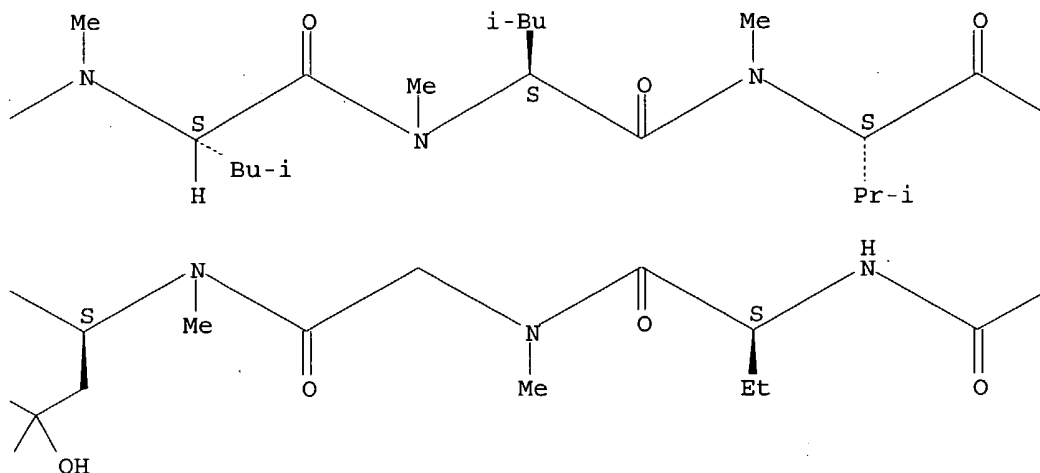
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

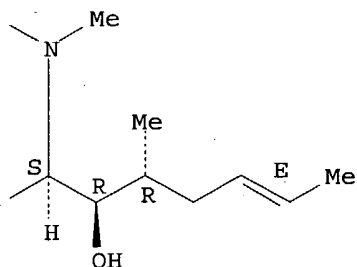


Me

PAGE 1-B



PAGE 1-C



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FILE 'USPATFULL' ENTERED AT 07:30:37 ON 13 APR 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 07:30:37 ON 13 APR 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> => d l66 bib ab kwic hitstr tot

L66 ANSWER 1 OF 16 USPATFULL on STN

AN 2004:83170 USPATFULL

TI Use of cyclosporin a 7-thioamide derivatives for hair growth

IN Kim, Sang-Nyun, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Ahn, Ho-Jeong, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Lee, Chang-Woo, Seo-gun Daejeon, KOREA, REPUBLIC OF

Kim, Seung-Jin, Seoul, KOREA, REPUBLIC OF

Lee, Min-Ho, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Kim, Chang-Deok, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Kim, Jung-Hun, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Kim, Jong-Il, Yusong-gu Daejeon, KOREA, REPUBLIC OF

Cho, Ho-Song, Seo-gu Daejeon, KOREA, REPUBLIC OF
 Lee, Heon-Sik, Yusong-gu Daejeon, KOREA, REPUBLIC OF

PI US 2004063626 A1 20040401
 AI US 2003-432448 A1 20031110 (10)
 WO 2001-KR1960 20011116
 PRAI KR 2000-69394 20001122
 DT Utility
 FS APPLICATION
 LREP Richard L Byrne, 700 Koppers Building, 436 Seventh Avenue, Pittsburg,
 PA, 15219-1818
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN 6 Drawing Page(s)
 LN.CNT 633

AB The present invention discloses a composition comprising a cyclosporin A derivative having an excellent hair revitalizing activity as an active ingredient, and more particularly, a composition comprising cyclosporin A 7-thioamide produced by chemical derivatization of cyclosporin A as an active ingredient for promoting hair growth.

SUMM [0001] The present invention relates to a hair growth promoter comprising a **cyclosporin** derivative as an active ingredient. More particularly, the present invention relates to a hair growth promoter comprising **cyclosporin A** 7-thioamide produced by chemical derivation of **cyclosporin A** as an active ingredient.

SUMM [0007] The **cyclosporin** family of drugs has immunosuppressive activity. It is also effective to inhibit growth of virus, fungus, protozoan, etc. and has . . . of periodontium, trichogenous effect, and so on, as side effects (Advances in Pharmacol., 1996, 35:114-246 and Drug Safety, 1994, 10:310-317). **Cyclosporin A**, a representative **cyclosporin**, is a cyclic peptide having the following Chemical Formula, which comprises 11 amino acids, including several N-methyl amino acids and. . .

SUMM [0009] The amino acid form of **cyclosporin A** of the above Chemical Formula 1 is L-configuration, unless otherwise specified. The residue numbering of amino acids starts from MeBmt. . . MeBmt and 11 for the last MeVal (N-methyl-L-valine) as shown in the Structure Formula 1. Nomenclature of various derivatives including **cyclosporins A** to Z, follows methods commonly used (Helv. Chim. Acta, 1987, 70:13-36). For example, **cyclosporins B** and **C**, in which only L- α aminobutyric acid, No. 2 residue of **cyclosporin A**, is substituted with L-alanine and L-threonine, respectively, are expressed by describing the different residues and the positions thereof, that is [Ala].sup.2 **cyclosporin** and [Thr].sup.2 **cyclosporin**.

SUMM [0010] Thioamide derivatives of **cyclosporin**, in which the carbonyl oxygen (O) of amino acid(s) of either No. 4 or No. 7 residue, or both is substituted with sulfur (S) are named as **cyclosporin** 4-thioamide ([.sup.4 ψ .sup.5 CS--NH] **cyclosporin**), **cyclosporin** 7-thioamide ([.sup.7 ψ .sup.8 CS--NH] **cyclosporin**), and **cyclosporin** 4,7-bis(thioamide) ([.sup.7 ψ .sup.8 CS--NH; .sup.4 ψ .sup.5 CS--NH] **cyclosporin**), according to known methods (Helv. Chim. Acta 1991, 74:1953-1990; J. Org. Chem. 1993, 58:673-677; and J. Org. Chem. 1994, 59:7249-7258).

SUMM [0011] So far, possible development of **cyclosporin** as a hair-regrowth agent has been studied by many research groups. Particularly, researches involving animal hair regrowth tests (Arch, Dermatol. . . and Am. J. Pathol., 1997, 150:1433-1441) have been widely conducted. In comparative experiments on mouse's back, it is shown that **cyclosporin** has a hair regrowth effect about 100 times superior to minoxidil. Based on such findings, there have been attempts to utilize **cyclosporin** as a treatment for male

pattern alopecia, and many applications for patents have been filed.

SUMM [0012] For example, Japanese Patent Publication Kokai Nos. Sho 60-243008, Sho 62-19512 and Sho 62-19513 disclose use of **cyclosporin** derivatives as a hair regrowth agent. Also, European Patent Publication No. 0414632 B1 discloses a **cyclosporin** derivatives with modified No. 8 residue, PCT Patent Publication No. WO 93/17039 and PCT Patent Publication No. WO 00/51558 disclose isocyclosporin and immunosuppressive **cyclosporin** derivatives, respectively. These **cyclosporins** and derivatives thereof are provided as a hair regrowth agent. Furthermore, in U.S. Pat. No. 5,807,820 and U.K. Patent No. 2,218,334 A, preparations containing **cyclosporins** with excellent transdermal absorption are suggested for new application of a hair regrowth agent.

SUMM . . . the present invention to provide a novel hair growth promoter having hair regrowth activity and selected from thioamide derivatives of **cyclosporin** having carbonyl oxygen (O) of either of amino acid(s) No. 4 or No. 7, or both substituted with sulfur (S). The thioamide derivatives of **cyclosporin** substituted with sulfur have been used for studies of various derivations of **cyclosporin** molecules (Helv. Chim. Acta 1991, 74:1953-1990, J. Org. Chem. 1993, 58:673-677 and J. Org. Chem. 1994, 59:7249-7258). The present inventors has synthesized three thioamide derivatives of **cyclosporin**: **cyclosporin** 7-thioamide ([.sup.7ψ.sup.8 CS--NH] **cyclosporin**), in which the carbonyl oxygen, (O) of amino acid No. 4 in the **cyclosporin** molecule is substituted with sulfur (S), **cyclosporin** 4-thioamide ([.sup.4ψ.sup.5 CS--NH] **cyclosporin**), in which the carbonyl oxygen (O) of amino acid No. 7 in the **cyclosporin** molecule is substituted with sulfur (S), and **cyclosporin** 4,7-bis(thioamide) ([.sup.7ψ.sup.8 CS--NH; .sup.4ψ.sup.5 CS--NH] **cyclosporin**, in which the carbonyl oxygens (O) of amino acids Nos. 4 and 7 are substituted with sulfur (S), and examined. . . regrowth effect. As a result, it was found that not all of those derivatives have hair regrowth effect, but only **cyclosporin** 7-thioamide ([.sup.7ψ.sup.8 CS--NH] **cyclosporin**, C.sub.62H.sub.111N.sub.11O.sub.11S) does have the hair regrowth effect.

SUMM [0015] Thus, the present invention is directed to, as a hair growth promoter, **cyclosporin** 7-thioamide ([.sup.7ψ.sup.8 CS--NH] **cyclosporin**, C.sub.62H.sub.111N.sub.11O.sub.11S) represented by the Chemical Formula 1. ##STR2##

SUMM [0020] D is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-valine;

SUMM [0022] F is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine;

SUMM [0025] H is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine;

SUMM [0026] I is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine; and

SUMM [0028] The preferred derivatives of **cyclosporin** of the above Chemical Formula 1 having hair regrowth activity are compounds represented by the following Chemical Formula 2. ##STR3##

SUMM [0033] C' is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-valine;

SUMM [0035] E' is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine;

SUMM [0038] G' is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine;

SUMM [0039] H' is N-methyl-L-leucine, γ -hydroxy-N-methyl-L-leucine, or L-leucine; and

SUMM [0041] The more preferred thioamide derivatives of **cyclosporin** of the above Chemical Formula 1 having hair regrowth activity are compounds represented by the following Chemical Formula 3. ##STR4##

SUMM [0054] The even more preferred thioamide derivatives of

cyclosporin of the above Chemical Formula 1 having hair regrowth activity are compounds represented by the following Chemical Formula 4.
##STR5##

SUMM [0064] The **cyclosporin A** 7-thioamide is a derivative of **cyclosporin A**, in which the carbonyl oxygen (O) of amino acid No. 7 in the **cyclosporin A** molecule is substituted with sulfur (S), that is, [⁷ψ.⁸CS--NH] (NH--CHCH.sub.3--CS--)**cyclosporin A** (C.sub.62H.sub.111N.sub.11O.sub.11S).

L66 ANSWER 2 OF 16 USPATFULL on STN

AN 2003:294781 USPATFULL

TI Use of 3-position cyclosporin derivatives for hair growth

IN Kim, Sang-Nyun, Jeonmin-Dong, KOREA, REPUBLIC OF

Ahn, Ho-Jeong, Jeonmin-Dong, KOREA, REPUBLIC OF

Lee, Chang-Woo, Mannyon-Dong, KOREA, REPUBLIC OF

Lee, Min-Ho, Doryong-Dong, KOREA, REPUBLIC OF

Kim, Jung-Hun, Eoeun-Dong, KOREA, REPUBLIC OF

Kim, Jong-Il, Jeonmin-Dong, KOREA, REPUBLIC OF

Kim, Seung-Jin, Seoul, KOREA, REPUBLIC OF

Cho, Ho-Song, Doryong-Dong, KOREA, REPUBLIC OF

Lee, Heon-Sik, Doryong-Dong, KOREA, REPUBLIC OF

Kim, Hyung-Jin, Doryong-Dong, KOREA, REPUBLIC OF

PI US 2003207798 A1 20031106

AI US 2002-303281 A1 20021125 (10)

RLI Division of Ser. No. US 2002-141723, filed on 9 May 2002, PENDING

PRAI KR 2001-25682 20010511

DT Utility

FS APPLICATION

LREP Richard L. Byrne, Webb Ziesenheim Logsdon Orkin & Hanson, P.C., 700 Koppers Building, 436 Seventh Avenue, Pittsburgh, PA, 15219-1818

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN 14 Drawing Page(s)

LN.CNT 1221

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a hair growth promoting agent including a cyclosporin derivative as an active ingredient, and more particularly, a hair growth promoting agent including a cyclosporin A derivative substituted in the 3-position as an active ingredient.

SUMM [0002] The present invention relates to a hair growth promoting agent comprising a **cyclosporin** derivative as an active ingredient and more particularly, to a hair growth promoting agent comprising **cyclosporin** derivatives modified in the 3-position as an active ingredient.

SUMM [0008] The **cyclosporin** family of drugs has immunosuppressive activity. It is also effective to inhibit growth of virus, fungus, protozoan, etc. and has various physiological effects such as nephrotoxicity, hepatotoxicity, hypertension, enlargement of periodontium, trichogenous effect, and so on, as side effects. **Cyclosporin A**, a representative **cyclosporin**, is a cyclic peptide having the following Chemical Formula, which comprises 11 amino acids, including several N-methyl amino acids and.

SUMM [0010] The amino acid form of **cyclosporin A** of the above Chemical Formula 1 is L-configuration, unless otherwise specified. The residue numbering of amino acids starts from MeBmt. . . MeBmt and 11 for the last MeVal (N-methyl-L-valine) as shown in the Structure Formula 1. Nomenclature of various derivatives including **cyclosporins A** to Z, follows methods commonly used (Helv. Chim. Acta, 1987, 70:13-36). For example, if Abu in the 2-position of **cyclosporin A** is substituted with L-alanine, L-threonine, L-valine or L-norvaline, the derivatives thus

prepared are named **cyclosporin B**, **cyclosporin C**, **cyclosporin D** or **cyclosporin G**, respectively. Further, when the amino acid residues of the **cyclosporin** derivatives differ from those of **cyclosporin A**, the derivatives are named by describing the substituent. For example, if sarcosine, being the amino acid residue 3 of **cyclosporin A**, is substituted with N-methyl-D-Abu.sup.3 or N-methyl-D-Nva.sup.3, the derivatives thus prepared are named [N-methyl-D-Abu.sup.3] **cyclosporin A** or [N-methyl-D-Nva.sup.3] **cyclosporin A**, respectively. Meanwhile, a common method for abbreviating amino acids is employed, that is, N-methyl-L-leucine is abbreviated by MeLeu, N-methyl-L-isoleucine by . . D-alanine by DAla, L-aminobutyric acid by Abu, L-threonine by Thr, and L-norvaline by Nva. Further, as for a derivative of **cyclosporin** which is substituted with sulfur instead of a carbonyl oxygen at the amino acid residue 7, the name of the derivative may be **cyclosporin 7-thioamide** or [.sup.7ψ.sup.8 CS--NH] **cyclosporin**, according to different references (Helv. Chim. Acta. 74: 1953-1990, 1991; J. Org. Chem. 58: 673-677, 1993; J. Org. Chem. 59:..

- SUMM [0011] So far, possible development of **cyclosporin** as a hair-regrowth agent has been studied by many research groups. Particularly, researches involving animal hair regrowth tests, human alopecia. . . models (Am. J. Pathol., 1997, 150:1433-1441) have been widely conducted. In comparative experiments on mouse's back, it is shown that **cyclosporin** has a hair regrowth effect about 100 times superior to minoxidil. Based on such findings, there have been attempts to utilize **cyclosporin** as a treatment for male pattern alopecia, and many applications for patents have been filed.
- SUMM [0012] For example, Japanese Patent Publication Kokai Nos. Sho 60-243008, Sho 62-19512 and Sho 62-19513 disclose use of **cyclosporin** derivatives as a hair regrowth agent. Also, Europe Patent Publication No. 0414632B1 teaches a **cyclosporin** derivative modified in the 8-position, and PCT Publication No. 93/17039 teaches isocyclosporin. Moreover, U.S. Pat. No. 5,807,820 and British Patent No. 2,218,334A disclose **cyclosporins** with excellent transdermal absorption, pursuant to the use of **cyclosporins** as hair restorers.
- SUMM [0013] Therefore, the present invention has been made in view of the above problems associated with side effects of **cyclosporin A**, and it is an object of the present invention to provide a hair growth promoting agent comprising a **cyclosporin** derivative as an active ingredient, which exerts an excellent hair growth-promotion ability.
- SUMM . . . and other objects can be accomplished by the provision of a hair growth promoting agent comprising a 3-position analog of **cyclosporin** represented by the below Formula 1, as an active ingredient, which is prepared by synthesizing a variety of derivatives thereof.
- SUMM [0024] D represents N-methyl-L-leucine, γ - **hydroxy N-methyl-L-leucine** or L-valine;
- SUMM [0034] I represents N-methyl-L-leucine, -γ - **hydroxy-N-methyl-L-leucine** or L-leucine;
- SUMM [0035] J represents N-methyl-L-leucine, -γ - **hydroxy-N-methyl-L-leucine** or L-leucine; and,
- SUMM . . . accordance with another aspect of the invention, there is provided a hair growth promoting agent comprising a 3-position analog of **cyclosporin** with an excellent hair growth promoting effect, represented by Formula 2 below, as an active ingredient.
- SUMM [0043] C' represents N-methyl-L-leucine, γ -

hydroxy-N-methyl-L-leucine or L-valine;
 SUMM [0045] E'represents N-methyl-L-leucine, γ - hydroxy N-methyl-L-leucine or L-leucine;
 SUMM [0048] H'represents N-methyl-L-leucine, γ - hydroxy N-methyl-L-leucine or L-leucine;
 SUMM [0049] I'represents N-methyl-L-leucine, γ - hydroxy N-methyl-L-leucine or L-leucine; and,
 SUMM . . . accordance with another aspect of the invention, there is provided a hair growth promoting agent comprising a 3-position analog of cyclosporin with an excellent hair growth promoting effect, represented by Formula 3 below, as an active ingredient,
 SUMM . . . aspect of the present invention, there is provided a hair growth promoting agent, whose composition comprising a 3-position analog of cyclosporin may be formulated in the form of liquid formulations, sprays, gels, pastes, emulsions, creams, conditioners or shampoos.

L66 ANSWER 3 OF 16 USPATFULL on STN

AN 2003:265840 USPATFULL

TI Use of 3-position cyclosporin derivatives for hair growth

IN Kim, Sang-Nyun, Jeonmin-dong, KOREA, REPUBLIC OF

Ahn, Ho-Jeong, Jeonmin-dong, KOREA, REPUBLIC OF

Lee, Chang-Woo, Mannyon-dong, KOREA, REPUBLIC OF

Lee, Min-Ho, Doryong-dong, KOREA, REPUBLIC OF

Kim, Jung-Hun, Eoeun-dong, KOREA, REPUBLIC OF

Kim, Jong-II, Jeonmin-dong, KOREA, REPUBLIC OF

Kim, Seung-Jin, Seoul, KOREA, REPUBLIC OF

Cho, Ho-Song, Doryong-dong, KOREA, REPUBLIC OF

Lee, Heon-Sik, Doryong-dong, KOREA, REPUBLIC OF

Kim, Hyung-Jin, Doryong-dong, KOREA, REPUBLIC OF

PA LG Household & Health Care Ltd., Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

PI US 2003186857 A1 20031002

AI US 2002-141723 A1 20020509 (10)

PRAI KR 2001-25682 20010511

DT Utility

FS APPLICATION

LREP Richard L. Byrne, 700 Koppers Building, 436 Seventh Avenue, Pittsburgh, PA, 15219-1818

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 14 Drawing Page(s)

LN.CNT 1276

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient, and more particularly, a hair growth promoting agent comprising a cyclosporin A derivative substituted in the 3-position as an active ingredient.

SUMM [0001] The present invention relates to a hair growth promoting agent comprising a cyclosporin derivative as an active ingredient and more particularly, to a hair growth promoting agent comprising cyclosporin derivatives modified in the 3-position as an active ingredient.

SUMM [0007] The cyclosporin family of drugs has immunosuppressive activity. It is also effective to inhibit growth of virus, fungus, protozoan, etc. and has various physiological effects such as nephrotoxicity, hepatotoxicity, hypertension, enlargement of periodontium, trichogenous effect, and so on, as side effects. Cyclosporin A, a representative cyclosporin,

is a cyclic peptide having the following Chemical Formula, which comprises 11 amino acids, including several N-methyl amino acids and.

- SUMM [0009] The amino acid form of **cyclosporin A** of the above Chemical Formula 1 is L-configuration, unless otherwise specified. The residue numbering of amino acids starts from MeBmt. . . MeBmt and 11 for the last MeVal (N-methyl-L-valine) as shown in the Structure Formula 1. Nomenclature of various derivatives, including **cyclosporins A** to **Z**, follows methods commonly used 10 (Helv. Chim. Acta, 1987, 70:13-36). For example, if Abu in the 2-position of **cyclosporin A** is substituted with L-alanine, L-threonine, L-valine or L-norvaline, the derivatives thus prepared are named **cyclosporin B**, **cyclosporin C**, **cyclosporin D** or **cyclosporin G**, respectively. Further, when the amino acid residues of the **cyclosporin** derivatives differ from those of **cyclosporin A**, the derivatives are named by describing the substituent. For example, if sarcosine, being the amino acid residue 3 of **cyclosporin A**, is substituted with N-methyl-D-Abu.sup.3 or N-methyl-D-Nva.sup.3, the derivatives thus prepared are named [N-methyl-D-Abu.sup.3] **cyclosporin A** or [N-methyl-D-Nva.sup.3] **cyclosporin A**, respectively. Meanwhile, a common method for abbreviating amino acids is employed, that is, N-methyl-L-leucine is abbreviated by MeLeu, N-methyl-L-isoleucine by . . D-alanine by DALa, L-aminobutyric acid by Abu, L-threonine by Thr, and L-norvaline by Nva. Further, as for a derivative of **cyclosporin** which is substituted with sulfur instead of a carbonyl oxygen at the amino acid residue 7, the name of the derivative may be **cyclosporin 7-thioamide** or [.sup.7ψ.sup.8 CS--NH] **cyclosporin**, according to different references (Helv. Chim. Acta. 74: 1953-1990, 1991; J. Org. Chem. 58:
- SUMM [0011] So far, possible development of **cyclosporin** as a hair-regrowth agent has been studied by many research groups. Particularly, researches involving animal hair regrowth tests, human alopecia. . . models (Am. J. Pathol., 1997, 150:1433-1441) have been widely conducted. In comparative experiments on mouse's back, it is shown that **cyclosporin** has a hair regrowth effect about 100 times superior to minoxidil. Based on such findings, there have been attempts to utilize **cyclosporin** as a treatment for male pattern alopecia, and many applications for patents have been filed.
- SUMM [0012] For example, Japanese Patent Publication Kokai Nos. Sho 60-243008, Sho 62-19512 and Sho 62-19513 disclose use of **cyclosporin** derivatives as a hair regrowth agent. Also, Europe Patent Publication No. 0414632B1 teaches a **cyclosporin** derivative modified in the 8-position, and PCT Publication No. 93/17039 teaches isocyclosporin. Moreover, U.S. Pat. No. 5,807,820 and British Patent No. 2,218,334A disclose **cyclosporins** with excellent transdermal absorption, pursuant to the use of **cyclosporins** as hair restorers.
- SUMM [0013] Therefore, the present invention has been made in view of the above problems associated with side effects of **cyclosporin A**, and it is an object of the present invention to provide a hair growth promoting agent comprising a **cyclosporin** derivative as an active ingredient, which exerts an excellent hair growth-promotion ability.
- SUMM . . . above and other objects can be accomplished by the provision of a hair growth promoting agent comprising a 3-position analog of **cyclosporin** represented by the below Formula 1, as an active ingredient, which is prepared by synthesizing a variety of derivatives thereof.
- SUMM [0024] D represents N-methyl-L-leucine, γ - hydroxy N-methyl-L-leucine or L-valine;

SUMM [0026] F represents N-methyl-L-leucine, γ -
hydroxy N-methyl-L-leucine or
 L-leucine;

SUMM [0034] I represents N-methyl-L-leucine, γ -
hydroxy-N-methyl-L-leucine or
 L-leucine;

SUMM [0035] J represents N-methyl-L-leucine, γ -
hydroxy-N-methyl-L-leucine or
 L-leucine; and,

SUMM . . . accordance with another aspect of the invention, there is
 provided a hair growth promoting agent comprising a 3-position analog of
cyclosporin with an excellent hair growth promoting effect,
 represented by Formula 2 below, as an active ingredient. ##STR3##

SUMM [0042] C' represents N-methyl-L-leucine, γ -
hydroxy-N-methyl-L-leucine or
 L-valine;

SUMM [0044] E' represents N-methyl-L-leucine, γ -
hydroxy N-methyl-L-leucine or
 L-leucine;

SUMM [0047] H' represents N-methyl-L-leucine, γ -
hydroxy N-methyl-L-leucine or
 L-leucine;

SUMM [0048] I' represents N-methyl-L-leucine, γ -
hydroxy N-methyl-L-leucine or
 L-leucine; and,

SUMM . . . accordance with another aspect of the invention, there is
 provided a hair growth promoting agent comprising a 3-position analog of
cyclosporin with an excellent hair growth promoting effect,
 represented by Formula 3 below, as an active ingredient, ##STR4##

SUMM . . . aspect of the present invention, there is provided a hair
 growth promoting agent, whose composition comprising a 3-position analog
 of **cyclosporin** may be formulated in the form of liquid
 formulations, sprays, gels, pastes, emulsions, creams, conditioners or
 shampoos.

CLM What is claimed is:

1. A hair growth promoting agent comprising a 3-position analog of
cyclosporin represented by Formula 1, as an active ingredient:
 ##STR5## in which A represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-
 L-threonine, (2S,3R,4R,6E)-3-sulfhydryl-4-methyl-2-(methylamino)-6-
 octenoic acid or (2S,4R,6E)-3-oxo-4-methyl-2-(methylamino)-6-octenoic
 acid; B. . . selected from the group consisting of amino, hydroxy,
 halo, haloalkyl, ester, alkoxy, cyano, nitro, alkylamino, and
 dialkylamino; D represents N-methyl-L-leucine, γ -
hydroxy N-methyl-L-leucine or
 L-valine; E represents L-valine or L-norvaline; F represents
 N-methyl-L-leucine, γ -**hydroxy N-**
methyl-L-leucine or L-leucine; G represents L-alanine
 or L-alanine thioamide ([.sup.7 ψ .sup.8CS--NH], NH--CHCH.sub.3--CS--);
 H represents a D-amino acid represented by the general formula. . .
 selected from the group consisting of amino, hydroxy, halo, haloalkyl,
 ester, alkoxy, cyano, nitro, alkylamino, and dialkylamino; I represents
 N-methyl-L-leucine, γ -**hydroxy-N-**
methyl-L-leucine or L-leucine; J represents
 N-methyl-L-leucine, γ -**hydroxy-N-**
methyl-L-leucine or L-leucine; and, K represents
 N-methyl-L-valine or L-valine.

2. The hair growth promoting agent as set forth in claim 1, wherein the
 3-position analog of **cyclosporin** is represented by Formula 2:
 ##STR6## in which MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-
 methyl-L-threonine; A' represents L-aminobutyric acid, L-alanine,
 L-threonine, L-valine or L-norvaline; B' represents
 N-methyl-D-aminobutyric acid, N-methyl-D-norvaline, D-2-

(methylamino)hexa-4-ynoyl, D-2-(methylamino)pent-4-ynoyl, D-2-methylthio-sarcosine, N-methyl-O-propenyl-D-serine or N-methyl-D-serine; C' represents N-methyl-L-leucine, γ - **hydroxy-N-methyl-L-leucine** or L-valine; D' represents L-valine or L-norvaline; E' represents N-methyl-L-leucine, γ - **hydroxy N-methyl-L-leucine** or L-leucine; F' represents L-alanine or L-alanine thioamide ([.sup.7ψ.sup.8CS--NH], NH--CHCH.sub.3--CS--); G' represents D-alanine or D-serine; H' represents N-methyl-L-leucine, γ - **hydroxy N-methyl-L-leucine** or L-leucine; I' represents N-methyl-L-leucine, γ - **hydroxy N-methyl-L-leucine** or L-leucine; and, MeVal represents N-methyl-L-valine.

3. The hair growth promoting agent as set forth in claim 1, wherein the 3-position analog of **cyclosporin** is represented by Formula 3:

##STR7## in which MeBmt represents N-methyl-(4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine; A" represents L-alanine, L-threonine, L-valine or L-norvaline; B" represents.

4. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Abu.sup.3] **cyclosporin A** as an active ingredient.

5. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Nva.sup.3] **cyclosporin A** as an active ingredient.

6. The hair growth promoting agent as set forth in claim 1, comprising [D-2-(methylamino)hexa-4-ynoyl.sup.3] **cyclosporin A** as an active ingredient.

7. The hair growth promoting agent as set forth in claim 1, comprising [D-2-(methylamino)pent-4-ynoyl.sup.3] **cyclosporin A** as an active ingredient.

8. The hair growth promoting agent as set forth in claim 1, comprising [D-2-methylthio-Sar.sup.3] **cyclosporin A** as an active ingredient.

9. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-O-propenyl-D-Ser.sup.3] **cyclosporin A** as an active ingredient.

10. The hair growth promoting agent as set forth in claim 1, comprising [N-methyl-D-Ser.sup.3] **cyclosporin A** as an active ingredient.

L66 ANSWER 4 OF 16 USPATFULL on STN

AN 2003:187403 USPATFULL

TI Tumor necrosis factor-gamma

IN Yu, Guo-Liang, Berkeley, CA, UNITED STATES

Ni, Jian, Germantown, MD, UNITED STATES

Rosen, Craig A., Laytonville, MD, UNITED STATES

Zhang, Jun, San Diego, CA, UNITED STATES

PI US 2003129189 A1 20030710

AI US 2002-226294 A1 20020823 (10)

RLI Continuation-in-part of Ser. No. US 2001-899059, filed on 6 Jul 2001, PENDING Continuation-in-part of Ser. No. US 2000-559290, filed on 27 Apr 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-246129, filed on 8 Feb 1999, PENDING Continuation-in-part of Ser. No. US 1998-131237, filed on 7 Aug 1998, PENDING Continuation-in-part of Ser. No. US

1998-5020, filed on 9 Jan 1998, ABANDONED Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, PENDING

PRAI US 2001-314381P 20010824 (60)
US 2001-278449P 20010326 (60)
US 2000-216879P 20000707 (60)
US 2000-180908P 20000208 (60)
US 1999-134067P 19990513 (60)
US 1999-132227P 19990503 (60)
US 1999-131963P 19990430 (60)
US 1998-74047P 19980209 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 49

ECL Exemplary Claim: 1

DRWN 33 Drawing Page(s)

LN.CNT 13325

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexpression of the TNF-gamma-alpha and/or TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

L66 ANSWER 5 OF 16 USPATFULL on STN

AN 2003:169089 USPATFULL

TI Cyclosporins

IN Ellmerer-Muller, Ernst, Innsbruck, AUSTRIA

Brossner, Dagmar, Innsbruck, AUSTRIA

Maslouh, Najib, Innsbruck, AUSTRIA

Ambrosi, Horst Dieter, Berlin, GERMANY, FEDERAL REPUBLIC OF

Jas, Gerhard, Berlin, GERMANY, FEDERAL REPUBLIC OF

Fischer, Gunter, Halle/Saale, GERMANY, FEDERAL REPUBLIC OF

PA C-Chem AG, Binningen, SWITZERLAND (non-U.S. corporation)

PI US 6583265 B1 20030624

AI US 2001-701542 20010108 (9)

PRAI EP 1998-110761 19980612

DT Utility

FS GRANTED

EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Lukton, David

LREP Wenderoth, Lind & Ponack, L.L.P.

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 1489

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel cyclosporins, processes for their preparation, their use as pharmaceuticals and pharmaceutical compositions comprising them. The novel cyclosporins are represented by the compound of formula I ##STR1##

or a pharmaceutically acceptable salt thereof, wherein the letters A to L represent residues of amino acids.

- SUMM The present invention relates to novel **cyclosporins**, processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them. Furthermore, this invention discloses a novel general method for the exchange of substituents at the sarcosine residue of the **cyclosporin** macrocycle.
- SUMM **Cyclosporin A** is well known for its immunosuppressive and antiinflammatory properties but many biological properties have been described in addition. EP 0 194 972 describes **cyclosporin** derivatives with substituents on the sarcosine in position 3 of the macrocycle, the introduction of such substituents, as well as the immunosuppressive, antiinflammatory and antiparasitic activity of these **cyclosporin** derivatives. EP 0 484 281 describes **cyclosporin** derivatives with reduced immuno-suppressive potency and activity against HIV.
- SUMM The present invention discloses novel **cyclosporins** which can be used for the treatment of infectious diseases, of chronic inflammatory and autoimmune diseases, to prevent cardiac hypertrophy, .
- SUMM A second embodiment of the present invention is a novel method to prepare **cyclosporins** with substituents at the sarcosine in position 3 of the macrocycle. EP 0 194 972 describes the introduction of certain substituents at the sarcosine. The method described in EP 0 194 972 involves treatment of a **cyclosporin** with strong base to generate a polyanion and subsequent reaction of this polyanion with electrophiles, such as disulfides, alkyl halides. . . . another. The present invention discloses such a method. In this novel method, a suitable substituent is first introduced into a **cyclosporin** polyanion and the resulting product is isolated. The substituent is subsequently activated to become a leaving group and replaced by. . . novel substituent. This novel method allows the introduction of a wide variety of substituents into the sarcosine residue of the **cyclosporin** macrocycle.
- SUMM The **cyclosporin** nomenclature and numbering systems used hereafter are those used by J. Kallen et al., "**Cyclosporins: Recent Developments in Biosynthesis, Pharmacology and Biology, and Clinical Applications**", Biotechnology, second edition, H.-J. Rehm and G. Reed, ed., 1997, . . .
- SUMM

Position Letter in
numbering Formula Amino acid in **cyclosporin A**

- 1 A N-Methyl-butenyl-threonine (MeBmt)
 - 2 B α -aminobutyric acid (Abu)
 - 3 C Sarcosine (Sar)
 - 4 D N-Methyl-leucine (MeLeu)
 - 5 E. . . .
- SUMM D N-methyl-leucine, **gamma-hydroxy-N-methyl-leucine**, N-methyl-valine, or N-methyl-isoleucine,
- SUMM Compounds of the formula I in which C is a sarcosine substituted by S--R₂ are prepared by forming polyanions from **cyclosporins** in which C is sarcosine and reacting these polyanions with appropriate sulfur electrophiles like disulfides, thiol-sulfinates, sulfenyl halides, or disulfide-derived sulfonium salts. The polyanions are in turn prepared by treating the **cyclosporins** in an appropriate solvent at low temperature with an excess of a strong base. Examples for strong bases are alkali. . . .
- SUMM . . . chloride. Such Bronsted or Lewis acids or metal salts convert S--R₂ or O--R'₃ substituents at the sarcosine position of the **cyclosporin** macrocycle into leaving groups, forming an intermediary cation of the formula VI which can then further react with

SUMM nucleophiles present. . . .
 . . . experts in the field and is analogous to the commonly accepted intermediate in the Mannich reaction. In the case of **cyclosporins**, however, such an intermediate has never been described and is new. Mannich reactions are used to introduce aminoalkyl residues into. . . pyrrol, or furane. Other nucleophiles reacting with such cations are allyl and vinylsilanes and -stannanes as well as acetylenes. Therefore, **cyclosporins** in which the amino acid residue of C is the cation of Formula VII are an especially preferred embodiment of. . . .
 SUMM . . . solutions, eye drops, or as gels and ointments. For topical and parenteral applications it is of special advantage that, unlike **cyclosporin A**, many of the compounds of the present invention have basic substituents which enable the formation of salts with physiologically acceptable. . . .

L66 ANSWER 6 OF 16 USPATFULL on STN

AN 2003:47754 USPATFULL

TI Nonimmunosuppressive [γ -hydroxy-methyllleucine⁴] cyclosporin A, hair growth stimulator and external composition for skin using the same

IN Kim, Sang-Nyun, Kaejeon, KOREA, REPUBLIC OF
 Ahn, Ho-Jeong, Daejeon, KOREA, REPUBLIC OF
 Kim, Myung-Kee, Daejeon, KOREA, REPUBLIC OF
 Kim, Jong-Il, Daejeon, KOREA, REPUBLIC OF
 Kim, Jung-Hun, Daejeon, KOREA, REPUBLIC OF
 Lee, Chang-Woo, Daejeon, KOREA, REPUBLIC OF
 Lee, Min-Ho, Daejeon, KOREA, REPUBLIC OF
 Kim, Chang-Deok, Daejeon, KOREA, REPUBLIC OF
 Cho, Ho-Song, Daejeon, KOREA, REPUBLIC OF
 Kim, Hyun-Sik, Daejeon, KOREA, REPUBLIC OF
 Jung, Min-Hwan, Daejeon, KOREA, REPUBLIC OF
 Kim, Seung-Jin, Seoul, KOREA, REPUBLIC OF

PA LG Chemical, Ltd., Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

PI US 6521595 B1 20030218

AI US 2000-580694 20000530 (9)

PRAI KR 1999-51646 19991119
 KR 2000-14837 20000323

DT Utility

FS GRANTED

EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Mohamed, Abdel A.

LREP Alston & Bird LLP

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 18 Drawing Page(s)

LN.CNT 597

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods for treating alopecia and stimulating hair growth and pharmaceutical compositions using nonimmunosuppressive [γ -hydroxy-methyllleucine^{sup.4}] cyclosporin A having superior hair growth-promoting effect, wherein the hydroxyl group is added to the carbon position of Number 4 methyllleucine of cyclosporin A by the microorganism.

IT 107335-26-2P
 (nonimmunosuppressive cyclosporin A derivative for hair growth)

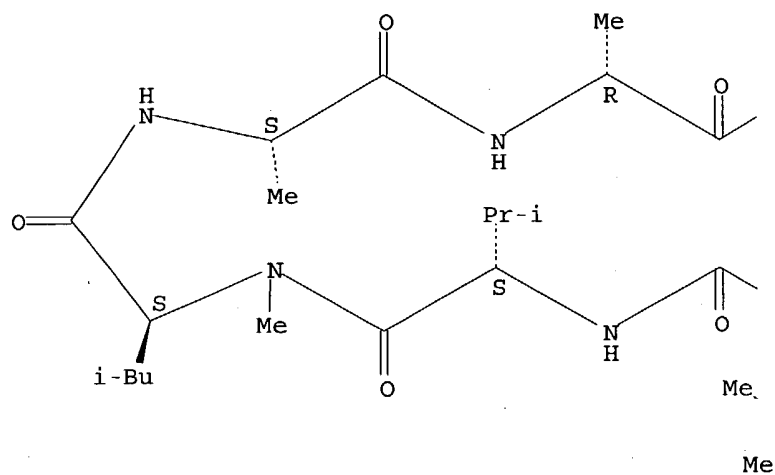
IT 107335-26-2P
 (nonimmunosuppressive cyclosporin A derivative for hair growth)

RN 107335-26-2 USPATFULL

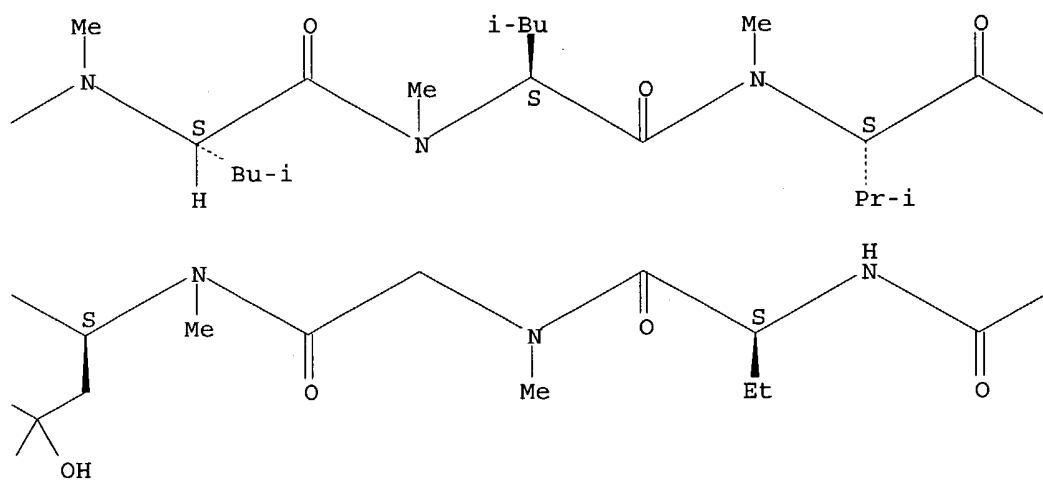
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

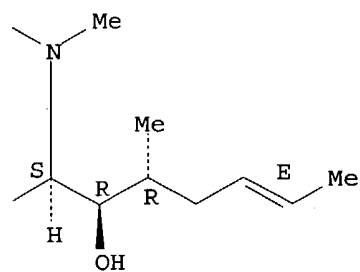
PAGE 1-A



PAGE 1-B



PAGE 1-C



L66 ANSWER 7 OF 16 USPATFULL on STN
 AN 2002:295088 USPATFULL
 TI Use of [**gamma-hydroxy-N-methyl-leucine**9] **cyclosporin a** for hair growth
 IN Kim, Sang-Nyun, Yusong-gu, KOREA, REPUBLIC OF
 Ahn, Ho-Jeong, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Chang-Woo, Seo-gu, KOREA, REPUBLIC OF
 Kim, Jung-Hun, Yusong-gu, KOREA, REPUBLIC OF
 Kim, Jong-Il, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Heon-Sik, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Min-Ho, Yusong-gu, KOREA, REPUBLIC OF
 Cho, Ho-Song, Seo-gu, KOREA, REPUBLIC OF
 Kim, Seung-Jin, Yusong-gu, KOREA, REPUBLIC OF
 Park, Hong-Soon, Yusong-gu, KOREA, REPUBLIC OF
 PI US 2002165133 A1 20021107
 AI US 2002-73021 A1 20020212 (10)
 PRAI KR 2001-7263 20010214
 DT Utility
 FS APPLICATION
 LREP VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP, P.O. BOX 34385, WASHINGTON,
 DC, 20043-9998
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN 5 Drawing Page(s)
 LN.CNT 577
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The present invention discloses a hair growth promoter comprising [**gamma.-hydroxy-N-methyl-L-leucine**.sup.9] **cyclosporin A**, in which a hydroxy group is added to a γ carbon of N-methyl-L-leucine at Number 9 position in **cyclosporin A** by metabolic action of a microorganism, as an active ingredient.
 TI Use of [**gamma-hydroxy-N-methyl-leucine**9] **cyclosporin a** for hair growth
 AB The present invention discloses a hair growth promoter comprising [**gamma.-hydroxy-N-methyl-L-leucine**.sup.9] **cyclosporin A**, in which a hydroxy group is added to a γ carbon of N-methyl-L-leucine at Number 9 position in **cyclosporin A** by metabolic action of a microorganism, as an active ingredient.
 SUMM [0001] The present invention relates to a hair growth promoter comprising a **cyclosporin** derivative as an active ingredient. More particularly, the present invention relates to a hair growth promoter comprising [γ -**hydroxy-N-methyl-L-leucine**.sup.9] **cyclosporin A** as an active ingredient.
 SUMM [0007] The **cyclosporin** family of drugs has immunosuppressive activity. It is also effective to inhibit growth of virus, fungus, protozoan, etc. and has various physiological effects such as neoprototoxicity, hepatotoxicity, hypertension, enlargement of periodontium, trichogenous effect, and so on, as side effects. **Cyclosporin A**, a representative **cyclosporin**, is a cyclic peptide having the following Chemical Formula, which comprises 11 amino acids, including several N-methyl amino acids and.
 SUMM [0017] The amino acid form of **cyclosporin A** of the above Chemical Formula 1 is L-configuration, unless otherwise specified. The residue numbering of amino acids starts from MeBmt. . . 1 for MeBmt and 11 for the last MeVal (N-methyl-L-valine) as shown in the Chemical Formula 1. The Nomenclature of **cyclosporin A** derivatives is practiced by describing the residue which is different from that of **cyclosporin A** and the position thereof. For example, a derivative in which N-methyl-L-leucine at No. 9 position

in cyclosporin A is substituted with .gamma
 .-hydroxy-N-methyl-L-leucine, is
 expressed as [γ -hydroxy-N-
 methyl-L-leucine.sup.9] cyclosporin

A. Also, residues are described following commonly used
 abbreviations. That is, MeLeu refers to N-methyl-L-leucine, MeIle refers
 to N-methyl-L-isoleucine, MeVal refers. . .

SUMM [0018] So far, possible development of cyclosporin as a
 hair-regrowth agent has been studied by many research groups.
 Particularly, researches involving animal hair regrowth tests, human
 alopecia. . . models (Am. J. Pathol., 1997, 150:1433-1441) have been
 widely conducted. In comparative experiments on mouse's back, it is
 shown that cyclosporin has a hair regrowth effect about 100
 times superior to minoxidil Based on such findings, there have been
 attempts to utilize cyclosporin as a treatment for male
 pattern alopecia, and many applications for patents have been filed.
 SUMM [0019] For example, Japanese Patent Publication Kokai Nos. Sho
 60-243008, Sho 62-19512 and Sho 62-19513 disclose use of
 cyclosporin derivatives as a hair regrowth agent. Also, European
 Patent Publication No. 0414632 B1 discloses a cyclosporin
 derivative with modified No. 8 residue, PCT Patent Publication No. WO
 93/17039 and PCT Patent Publication No. WO 00/51558 disclose
 isocyclosporin and immunosuppressive cyclosporin derivatives,
 respectively. These cyclosporins and derivatives thereof are
 provided as a hair regrowth agent. Furthermore, in U.S. Pat. No.
 5,807,820 and U.K. Patent No. 2,218,334 A, preparations containing
 cyclosporins with excellent transdermal absorption are suggested
 for new application of a hair regrowth agent. However, the all
 cyclosporins used in the above documents have strong
 immunosuppressive ability and hence, they have limits in use for
 treatment of general. . . hair loss, despite their excellent hair
 regrowth effect. Recently, in WO 0051558 a method for treating hair loss
 using nonimmunosuppressive cyclosporin derivatives is
 disclosed. However, the structure of [γ -hydroxy
 -N-methyl-L-leucine.sup.9]
 cyclosporin A claimed in the present invention is not
 included.

SUMM . . . hair growth promoter without problems involved in the prior
 art, the present inventors have examined the main metabolic products of
 cyclosporin for their hair growth effect, while considering
 their potential immunosuppressive properties. The main metabolites
 examined include M17, a metabolite wherein. . . found that only the
 M1 showed an excellent hair growth effect while having reduced
 immunosuppressiveness. The M1 is named as [γ -hydroxy-N-methyl-L-
 leucine.sub.9]cyclosporin A according to the common
 nomenclature, and its immunosuppressiveness is known to be lower than
 that of cyclosporin A (see, Transplantation 1987;
 43:123-127, Clin. Chem. 1990; 36:225-229, and Transplant. Proc. 1988;
 20:575-584).

SUMM . . . Thus, the above present invention is directed to a hair growth
 promoter comprising, as an active ingredient, a metabolite of
 cyclosporin A, that is [γ -
 hydroxy-N-methyl-L-leucine.sup.9]

cyclosporin A, in which a hydroxy group is added to a
 γ carbon of No. 9 residue MeLeu, and represented by the. . .

SUMM [0026] D is N-methyl-L-leucine, γ -hydroxy-
 N-methyl-L-leucine, or L-valine;

SUMM [0028] F is N-methyl-L-leucine, γ -hydroxy-
 N-methyl-L-leucine, or L-leucine;

SUMM [0031] OHMeLeu is γ -hydroxy-N-
 methyl-L-leucine;

SUMM [0032] I is N-methyl-L-leucine, γ -hydroxy-
 N-methyl-L-leucine, or L-leucine; and

SUMM [0034] The preferred metabolites of **cyclosporin** of the above Chemical Formula 1 having hair regrowth activity are compounds, [**gamma.-hydroxy-N-methyl-L-leucin.sup.9]cyclosporin A**, represented by the following formula (II). ##STR3##

SUMM [0039] C' is N-methyl-L-leucine, **gamma -hydroxy-N-methyl-L-leucine**, or L-valine;

SUMM [0041] E' is N-methyl-L-leucine, **gamma -hydroxy-N-methyl-L-leucine**, or L-leucine;

SUMM [0044] OHMeLeu is **gamma -hydroxy-N-methyl-L-leucine**;

SUMM [0045] H' is N-methyl-L-leucine, **gamma -hydroxy-N-methyl-L-leucine**, or L-leucine; and

SUMM [0047] The more preferred [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** of the above Chemical Formula 1 having hair regrowth activity are compounds represented by the following formula (III). ##STR4##

SUMM [0057] OHMeLeu is **gamma -hydroxy-N-methyl-L-leucine**;

SUMM [0060] The even more preferred [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** of the above Chemical Formula 1 having hair regrowth activity are compounds represented by the following formula (IV). ##STR5##

SUMM [0068] OHMeLeu is **gamma -hydroxy-N-methyl-L-leucine**; and

SUMM . . . invention is directed to a liquid formulation, spray, gel, paste, emulsion, cream, conditioner, or shampoo formulated from the composition comprising [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** as an active ingredient having a hair growth promoting effect.

DRWD [0072] FIG. 1 is a result of a High Pressure Liquid Chromatography of [**gamma.-hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A**;

DRWD [0073] FIG. 2 is a .sup.1H-NMR spectrum of [**gamma-hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A**;

DRWD [0074] FIG. 3 is a .sup.13C-NMR spectrum of [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A**;

DRWD [0075] FIG. 4 is a photograph of a control group in the animal test measuring hair growth effects of **cyclosporin A** and [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** using C57BL/6 mice;

DRWD [0076] FIG. 5 is a photograph of a group treated with **cyclosporin A** in the animal test measuring hair growth effects of **cyclosporin A** and [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** using C57BL/6 mice; and

DRWD [0077] FIG. 6 is a photograph of a group treated with [**gamma-hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** in the animal test measuring hair effects of **cyclosporin A** and [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** using C57BL/6 mice.

DETD . . . in detail as follows. In order to develop a novel hair regrowing agent, the present inventors produced various metabolites of **cyclosporin** and carried out the hair regrowth evaluation tests for the metabolites. As a result, it was found that [**gamma -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin A** has an superior hair regrowth (restoring) effect than any other compounds.

DETD . . . trifluoroacetic acid(TFA). The product was then subjected to a cyclization reaction using benzotriazol-1-yl-oxy-tris-(dimethylamino)-

phosphonium hexafluorophosphate and dimethylaminopyridine to form a substituted **cyclosporin A**-acetate, which was treated with sodium methoxide (NaOMe) to remove acetyl groups. In this way, the metabolite M21, [Leu.sup.4]**cyclosporin A**, wherein a methyl group is removed from the No. 4 N-methyl-L-leucine was produced. M21 was found to have no hair. . . .

DETD [0082] The hydroxy group at No. 1 position in **cyclosporin A** was reacted with acetic anhydride to synthesize [O-acetyl] 1 **cyclosporin A**. The product was refluxed with N-bromosuccinimide in the presence of a catalyst of azobisisobutyronitrile to synthesize [O-acetyl-6-bromo] 1 **cyclosporin A**. The product was added to a solvent of ethyl methyl ketone and heated in the presence of a catalyst mixture of tetrabutylammonium acetate and sodium iodide to synthesize [6-acetoxy-O-acetyl] 1 **cyclosporin A**. The product was deacetylated with 0.5M sodium methoxide to synthesize M17. The resulting M17 was identified by Mass spectroscopy and. . . .

DETD Preparation of [γ -**Hydroxy-N-Methyl-L-Leucine**.sup.9]**cyclosporin A**

DETD [0083] In this example, preparation of [γ -**hydroxy-N-methyl-L-leucine**.sup.9]**cyclosporin A** showing hair regrowth effect after being transformed by microorganisms will be described.

DETD [0084] *Pseudonocardia autotrophica* KCTC 9441 was used as a strain for preparing the metabolite of **cyclosporin A**. The strain was cultured in a medium containing 0.7% glucose, 0.45% yeast extract, 0.5% malt extract, 1.0% soluble starch and. . . .

DETD culture was performed in a 4 l fermentor using the above-described medium. At 24 hour after the actual culture started, **cyclosporin A** dissolved in methanol was added to a concentration of 100 mg/l and culturing was continued for a further 72 hours. . . . the organic phase was concentrated. The concentrate was separated and fractionated by liquid chromatography. The liquid chromatography elution profile showing **cyclosporin** derivatives is shown in FIG. 1. In FIG. 1, the peak observed at 22 to 23 minutes of retention time corresponds to **cyclosporin A** and the peak at 15 minutes corresponds to [γ -**hydroxy-N-methyl-L-leucine**.sup.9]**cyclosporin A**.

DETD [0087] Also, the [γ -**hydroxy-N-methyl-L-leucine**.sup.9]**cyclosporin A** can be prepared using microsomal enzyme from rabbit liver.

DETD 0.1 M phosphate buffered saline. The resulting solution was used as an enzyme source. The prepared microsomal enzyme (50 mg), **cyclosporin** (1 mg) and NADPH (5 mM) were added to distilled water of an appropriate amount and reacted in a thermostatic. . . .

DETD Analysis of Structure of [γ -**Hydroxy-N-Methyl-L-Leucine**.sup.9]**cyclosporin A**

DETD [0089] [γ -**hydroxy-N-methyl-L-leucine**.sup.9]**cyclosporin A** (C.sub.62H.sub.111N.sub.11O.sub.13) was analyzed according to FAB MS (ZMS AX 505H) and a peak was observed at m/z 1219 [M+H].sup.+, which. . . .

DETD Preparation of a Hair Revitalizing Tonic Containing [γ -**Hydroxy-N-Methyl-L-leucine**.sup.9]**cyclosporin A**

DETD animal test, it was shown that Composition 1 has hair regrowth effect comparable to a hair revitalizing tonic containing 0.1% **cyclosporin A**.

TABLE 1

Ingredients	Composition 1	Composition 2	Composition 3
Ethanol	40.0	40.0	40.0
[γ -hydroxy-N-methyl-L-leucine.sup.9]	0.1	1.0	8.0
cyclosporin A			
Tocopherol acetate	0.1	0.1	0.1
Salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Tween 20	0.5	0.5	0.5
Fragrance	Prop. Amount	Prop. Amount	Prop.. . .
DETD	Preparation of a Hair Cream Containing [γ -Hydroxy-N-Methyl-L-Leucine.sup.9] cyclosporin A		
DETD	. . . 1 described later. In the animal test, it was shown that Composition 1 described in Table 2, which contains 0.1% [γ -hydroxy-N-methyl-L-leucine.sup.9]cyclosporin containing 0.1% cyclosporin A .		

TABLE 2

Ingredients	Composition 1	Composition 2	Composition 3
Paraffin	5.0	5.0	5.0
Setostearylalcohol	5.5	5.5	5.5
Petrolatum	5.5	5.5	5.5
Glycerine-monostearate	3.0	3.0	3.0
Polyoxyethylene octyldodecylether	3.0	3.0	3.0
Propylparaben	0.3	0.3	0.3
[γ -hydroxy-N-methyl-L-leucine.sup.9]	0.1	1.0	8.0
cyclosporin A			
Glycerin	7.0	7.0	7.0
Dipropylene glycol	20.0	20.0	20.0
Polyethyleneglycol	5.0	5.0	5.0
Water	q.s. to 100 wt % without fragrance and colorant		
Fragrance	Prop. Amount. . .		
DETD	Preparation of a Shampoo Containing [γ -Hydroxy-N-Methyl-L-Leucine.sup.9] cyclosporin A		
DETD	. . . aqueous solution)		
Palm oil fatty acid	3.0	3.0	3.0
Diethanolamide			
propylene glycol	2.0	2.0	2.0
Methyl	0.2	0.2	0.2
paraoxybenzoic acid			
Ethanol	2.0	2.0	2.0
[γ -hydroxy-N-methyl-L-leucine.sup.9]	1.0	3.0	10.0
cyclosporin A			
Salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	0.3
Fragrance	Prop. Amount	Prop. Amount	Prop. Amount
Colorant	Prop. Amount	Prop. Amount	Prop. Amount
Water	q.s.. . .		
DETD	Preparation of a Hair Conditioner Containing [γ -Hydroxy-N-Methyl-L-leucine.sup.9]		

cyclosporin A

DETD . . . conditioner.

TABLE 4

Ingredients	Composition 1	Composition 2	Composition 3
Cetanol	3.0	3.0	3.0
Self-emulsifiable	2.0	2.0	3.0
Glycerol-monostearate			
Squalene	10.0	10.0	10.0
[γ -hydroxy-N-methyl-L-leucine.sup.9]	1.0	5.0	10.0
cyclosporin A			
Propylene glycol	2.0	2.0	2.0
Stearyl dimethyl Benzylammonium chloride (25 wt % aqueous solution)	8.0	8.0	8.0
Methyl paraoxybenzoic acid	0.2	0.2	0.2
Salicylic acid	0.3	0.3	0.3
L-menthol	0.3	0.3	

DETD Test of Hair Regrowth Effects of [γ -hydroxy-N-Methyl-L-Leucine.sup.9]**cyclosporin A**

DETD . . . electric shaver, and weighed. The mice were divided into several groups with weights equally distributed. After one day of adaptation, **cyclosporin A**, main metabolites of **cyclosporin A**, such as [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A**, M17, M21, and control were applied over the hair removed area once a day per each individual for 30 days. Here, the applied amount of **cyclosporin A** and metabolites thereof was 100 μ l (0.05% w/v). The degree of hair growth were judged by naked eye and the . . . photographed. FIG. 4 shows a photograph of a control group in the animal test for measuring hair growth effects of **cyclosporin A** and [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A** using C57BL/6 mice. FIG. 5 shows a photograph of a group treated with **cyclosporin A** in the test for measuring hair growth effects of **cyclosporin A** and [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A** using C57BL/6 mice. FIG. 6 shows a photograph of a group treated with [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A** in the test for measuring hair growth effects of **cyclosporin A** and [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A** using C57BL/6 mice, in which it is noted that the result is comparable to that of **cyclosporin A**, that is before transformation. In the mean time, metabolites M17 and M21 show no significant effect.

DETD Test of Immunosuppression of [γ -Hydroxy-N-Methyl-L-Leucine.sup.9]**cyclosporin A**

DETD . . . untreated reactive cell group. The resulting mixture was incubated for 4 days. During the incubation, the mixture was treated with **cyclosporin A** and derivatives thereof to be examined including [γ -hydroxy-N-methyl-L-leucine.sup.9]**cyclosporin A**

in serial dilutions from 10.sup.-6 M to 10.sup.-11 M. After 4 days incubation, .sup.3H-thymidine was added to the mixtures and. . . hours. Then, the amount of thymidine introduced into the cells was measured (liquid scintillation counter) and IC.sub.50 (µg/ml) of respective **cyclosporins** were calculated.

DETD [0100] As a result, IC.sub.50 (µg/ml) of **cyclosporin A** was found to be 0.035, 0.025 and 0.030, while [**gamma** .-hydroxy-N-methyl-L-leucine

.sup.9]**cyclosporin A** was 0.165, 0.178 and 0.150.

Thus, it was noted that [**gamma** -hydroxy-N

-methyl-L-leucine.sup.9]**cyclosporin**

A had lower immunosuppressive effect than **cyclosporin**

A, which accorded with the data in the literature

(Transplantation 1987, 43:123-127)

DETD . . . cell proliferation against stimulation by PHA, to mononuclear cells (4+10.sup.6/ml) which had been treated with PHA (10 µg/ml) were added **cyclosporin A** and derivatives thereof including [**gamma** -hydroxy-N-

-methyl-L-leucine.sup.9]**cyclosporin A**

in serial dilutions from 10.sup.-6 M to 10.sup.-11 M, followed by

incubation for 3 days. Then, like in the MLR. . . was added to the

cells, which were again incubated for additional 16 hours. After the

incubation, IC.sub.50 (µg/ml) of respective **cyclosporins**

were calculated. IC.sub.50 (µg/ml) of **cyclosporin A**

was 0.25, 0.45 and 0.32, while [**gamma**.hydroxy-

N-methyl-L-leucine.sup.9]**cyclosporin**

A was 1.23, 2.25 and 1.50. Thus, it was noted that [.

gamma.-hydroxy-N-methyl-L-

leucine.sup.9]**cyclosporin A** had lower

immunosuppressive effect than **cyclosporin A**.

DETD [0104] A hair growth promoter comprising [**gamma** -hydroxy-N-methyl-L-leucine.sup.9]

cyclosporin A as an active ingredient according to the

present invention has excellent hair growth promoting effect, leading

the superior hair restoring. . .

CLM What is claimed is:

1. A hair growth promoter comprising [**gamma** -hydroxy

-N-methyl-L-leucine.sup.9]

cyclosporin A as an active ingredient.

L66 ANSWER 8 OF 16 USPATFULL on STN

AN 2002:272419 USPATFULL

TI Tumor necrosis factor-gamma

IN Yu, Guo-Liang, Berkeley, CA, UNITED STATES

Ni, Jian, Germantown, MD, UNITED STATES

Rosen, Craig A., Laytonville, MD, UNITED STATES

Zhang, Jun, Bethesda, MD, UNITED STATES

PI US 2002150534 A1 20021017

AI US 2001-899059 A1 20010706 (9)

RLI Continuation-in-part of Ser. No. WO 2000-US11689, filed on 28 Apr 2000, UNKNOWN Continuation-in-part of Ser. No. US 1999-246129, filed on 8 Feb 1999, PENDING Continuation-in-part of Ser. No. US 1998-131237, filed on 7 Aug 1998, PENDING Continuation-in-part of Ser. No. US 1998-5020, filed on 9 Jan 1998, ABANDONED Continuation-in-part of Ser. No. US 1995-461246, filed on 5 Jun 1995, ABANDONED Continuation-in-part of Ser. No. WO 1994-US12880, filed on 7 Nov 1994, UNKNOWN

PRAI US 2001-278449P 20010326 (60)

US 2000-216879P 20000707 (60)

US 2000-180908P 20000208 (60)

US 1999-134067P 19990513 (60)

US 1999-132227P 19990503 (60)

US 1999-131963P 19990430 (60)

US 1998-74047P 19980209 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 49
ECL Exemplary Claim: 1
DRWN 33 Drawing Page(s)
LN.CNT 12881

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Human TNF-gamma-alpha and TNF-gamma-beta polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing such polypeptides to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma-alpha and TNF-gamma-beta nucleic acid sequences or overexpression of the TNF-gamma-alpha and/or TNF-gamma-beta polypeptides. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.

L66 ANSWER 9 OF 16 USPATFULL on STN

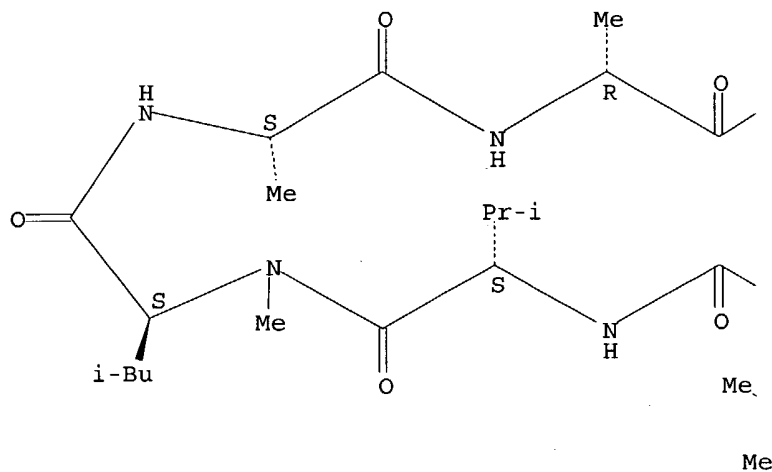
AN 2001:165815 USPATFULL
TI Novel process for the preparation of cyclosporin derivatives
IN Viskov, Christian, Ris Orangis, France
PI US 2001025025 A1 20010927
AI US 2000-742008 A1 20001222 (9)
RLI Continuation of Ser. No. WO 1999-FR1480, filed on 21 Jun 1999, UNKNOWN
PRAI FR 1998-7846 19980622
DT Utility
FS APPLICATION
LREP Finnegan, Henderson, Farabow,, Garrett & Dunner L.L.P., 1300 I Street, N.W., Washington, DC, 20005-3315
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1434

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

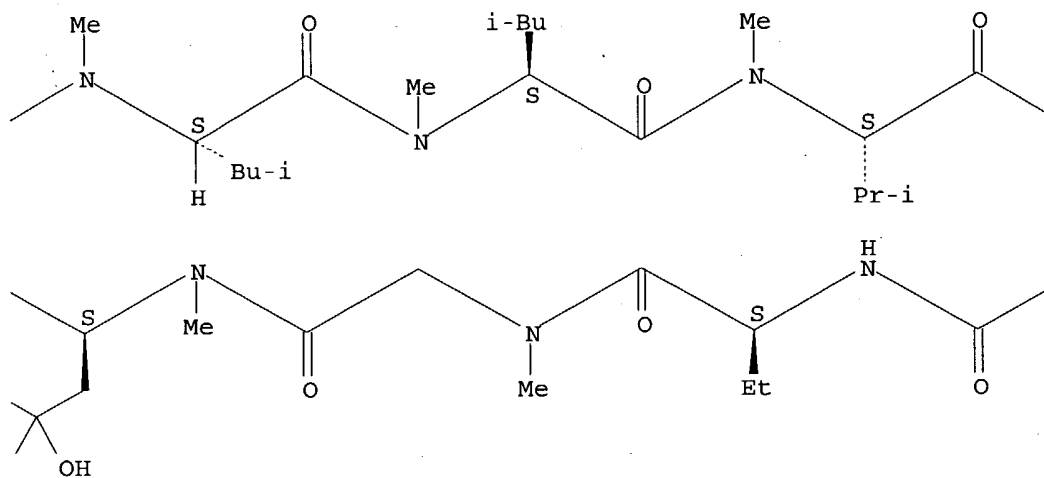
AB The invention concerns a novel method for preparing an intermediate polyanion for preparing cyclosporin derivatives by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide. The treated cyclosporin has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position a and/or any other acid group capable of deprotonation which are optionally deprotonated or in protected form.
IT 624-92-0, Dimethyl disulfide 1072-11-3 7647-17-8, Cesium chloride, reactions 59865-13-3, Cyclosporine A 107335-26-2
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
IT 107335-26-2
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
RN 107335-26-2 USPATFULL
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

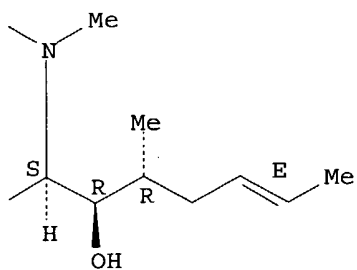
PAGE 1-A



PAGE 1-B



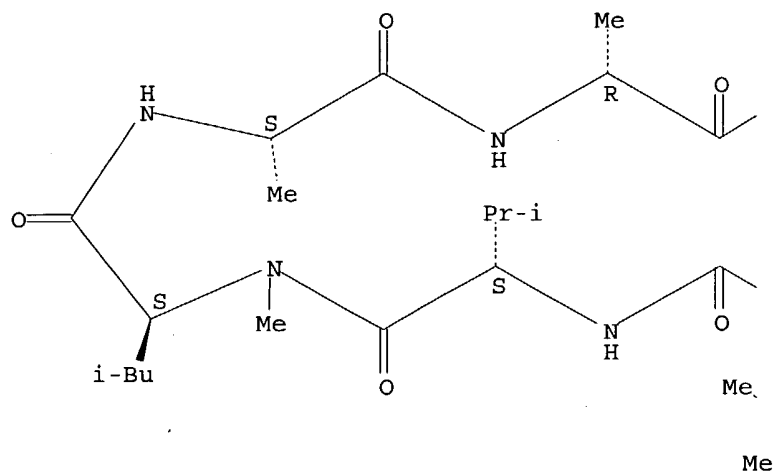
PAGE 1-C



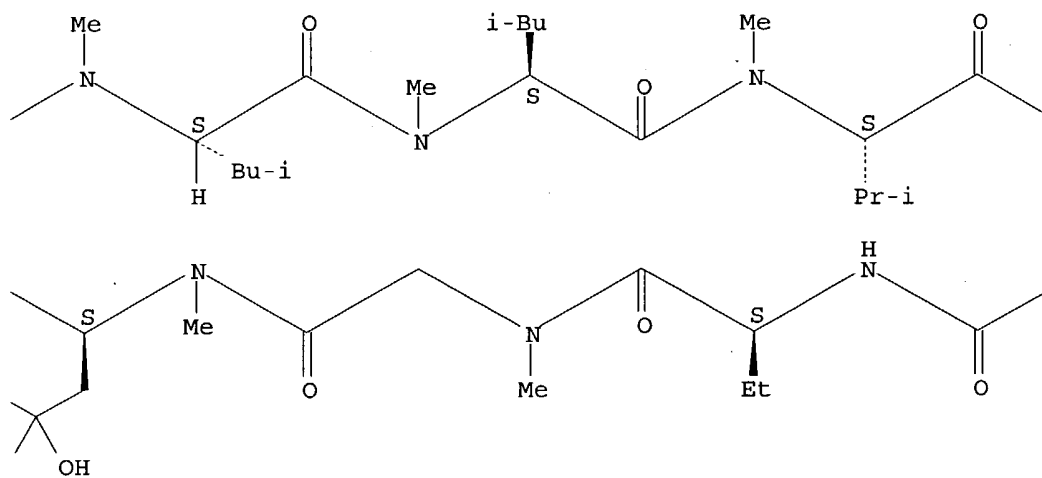
L66 ANSWER 10 OF 16 USPATFULL on STN
AN 2001:102610 USPATFULL
TI Cyclosporin fermentation process
IN Ko, Soo Young, London, United Kingdom
Kobel, Hans, Basel, Switzerland
Besemer-Rosenwirth, Brigitte, Modling, Austria
Seebach, Dieter, Zurich, Switzerland
Traber, ReneP., Basel, Switzerland
Wenger, Roland, Riehen, Switzerland
Bollinger, Pietro, Bottmingen, Switzerland
PA Novartis AG, Basel, Switzerland (non-U.S. corporation)
PI US 6255100 B1 20010703
AI US 1999-392282 19990909 (9)
RLI Division of Ser. No. US 1998-84709, filed on 26 May 1998, now patented,
Pat. No. US 5981479 Division of Ser. No. US 1995-427312, filed on 24 Apr
1995, now patented, Pat. No. US 5767069 Continuation of Ser. No. US
1994-232795, filed on 25 Apr 1994, now abandoned Continuation of Ser.
No. US 1993-57067, filed on 3 May 1993, now abandoned Continuation of
Ser. No. US 1991-785959, filed on 31 Oct 1991, now abandoned
PRAI GB 1990-23859 19901102
GB 1990-23970 19901105
GB 1990-23971 19901105
GB 1990-23972 19901105
GB 1991-16836 19910805
DT Utility
FS GRANTED
EXNAM Primary Examiner: Wessendorf, T. D.
LREP Lopez, Gabriel
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 809
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB It has been found that nonimmunosuppressive, cyclophilin-binding
cyclosporins are useful in the treatment and prevention of AIDS and
AIDS-related disorders. Such cyclosporins include novel Ciclosporin
derivatives modified at the 4- and/or 5-positions.
IT 59865-13-3P, Cyclosporin A 79217-60-0P, Cyclosporin 89270-25-7P
89270-28-0P 107335-26-2P 143205-41-8P 143205-43-0P
143205-44-1P 143205-45-2P 143222-39-3P 143222-40-6P
(preparation of, as HIV inhibitor, AIDS treatment in relation to)
IT 107335-26-2P
(preparation of, as HIV inhibitor, AIDS treatment in relation to)
RN 107335-26-2 USPATFULL
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

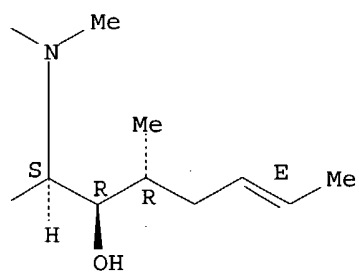
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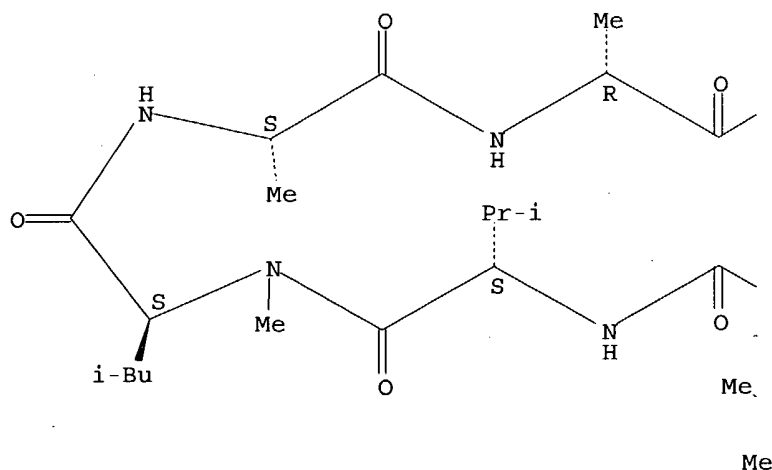
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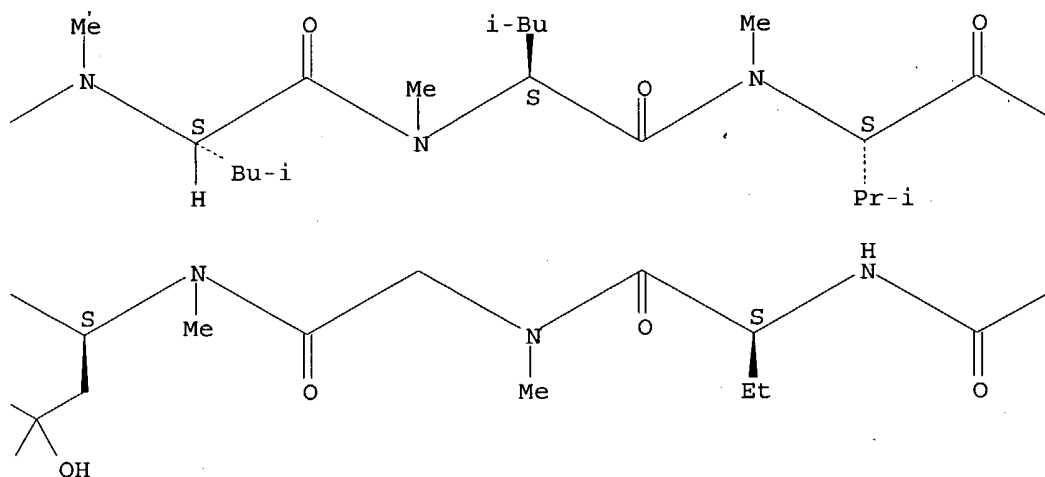
L66 ANSWER 11 OF 16 USPATFULL on STN
 AN 1999:155682 USPATFULL
 TI Cyclosporin compounds, their preparation and the pharmaceutical compositions which contain them
 IN Barriere, Jean-Claude, Bures sur Yvette, France
 Bashiardes, Georges, Thiais, France
 Carry, Jean-Christophe, Meudon, France
 Evers, Michel, La Queue En Brie, France
 Filoche, Bruno, Creteil, France
 Mignani, Serge, Chatenay-Malabry, France
 PA Rhone-Poulenc Rorer, S.A., Antony Cedex, France (non-U.S. corporation)
 PI US 5994299 19991130
 AI US 1997-997612 19971223 (8)
 PRAI FR 1996-15955 19961224
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Tsang, Cecilia J.
 LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
 CLMN Number of Claims: 22
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 1302
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Cyclosporin compounds of formula (I): ##STR1## wherein Alk and R are as defined herein, or a pharmaceutically acceptable salt thereof, which derivatives are useful in the treatment and/or prophylaxis of retrovirus infections.
 IT 1072-11-3, Bis[2-(dimethylamino)ethyl] disulfide 107335-26-2
 (preparation of cyclosporin derivs. and their pharmaceutical compns.)
 IT 107335-26-2
 (preparation of cyclosporin derivs. and their pharmaceutical compns.)
 RN 107335-26-2 USPATFULL
 CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

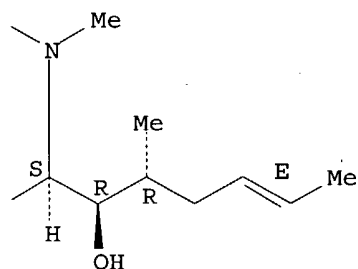
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PAGE 1-B



PAGE 1-C



L66 ANSWER 12 OF 16 USPATFULL on STN
 AN 1999:141886 USPATFULL
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 IN Ko, Soo Young, London, United Kingdom
 Kobel, Hans, Basel, Switzerland
 Besemer-Rosenwirth, Brigitte, Modling, Austria
 Seebach, Dieter, Zurich, Switzerland
 Traber, Rene P., Basel, Switzerland
 Wenger, Roland, Riehen, Switzerland
 Bollinger, Pietro, Bottmingen, Switzerland
 PA Novartis AG, Basel, Switzerland (non-U.S. corporation)
 PI US 5981479 19991109
 AI US 1998-84709 19980526 (9)
 RLI Division of Ser. No. US 1995-427312, filed on 24 Apr 1995, now patented,
 Pat. No. US 5767069
 PRAI GB 1990-23859 19901102
 GB 1990-23970 19901105
 GB 1990-23971 19901105
 GB 1990-23972 19901105
 GB 1991-16836 19910805
 DT Utility
 FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.
 LREP Lopez, Gabriel, Furman, Diane E.
 CLMN Number of Claims: 12
 ECL Exemplary Claim: 1
 DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
 LN.CNT 841

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB It has been found that nonimmunosuppressive, cyclophilin-binding cyclosporins are useful in the treatment and prevention of AIDS and AIDS-related disorders. Such cyclosporins include novel Ciclosporin derivatives modified at the 4- and/or 5-positions.

IT 59865-13-3P, Cyclosporin A 79217-60-0P, Cyclosporin 89270-25-7P
 89270-28-0P **107335-26-2P** 143205-41-8P 143205-43-0P
 143205-44-1P 143205-45-2P 143222-39-3P 143222-40-6P
 (preparation of, as HIV inhibitor, AIDS treatment in relation to)

IT **107335-26-2P**
 (preparation of, as HIV inhibitor, AIDS treatment in relation to)

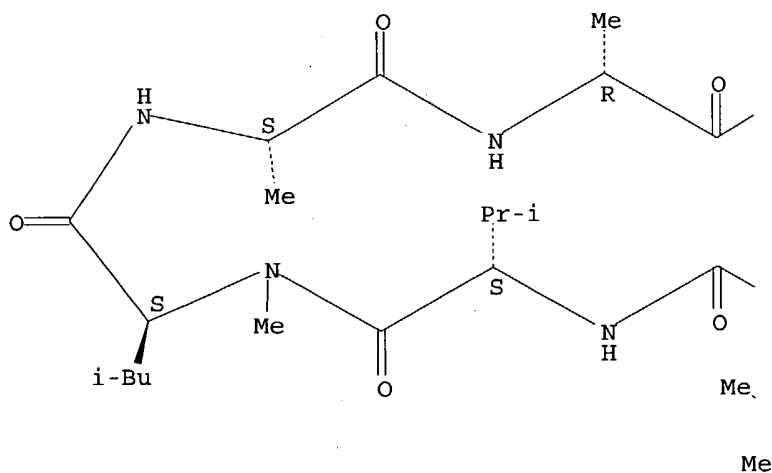
RN 107335-26-2 USPTAFULL

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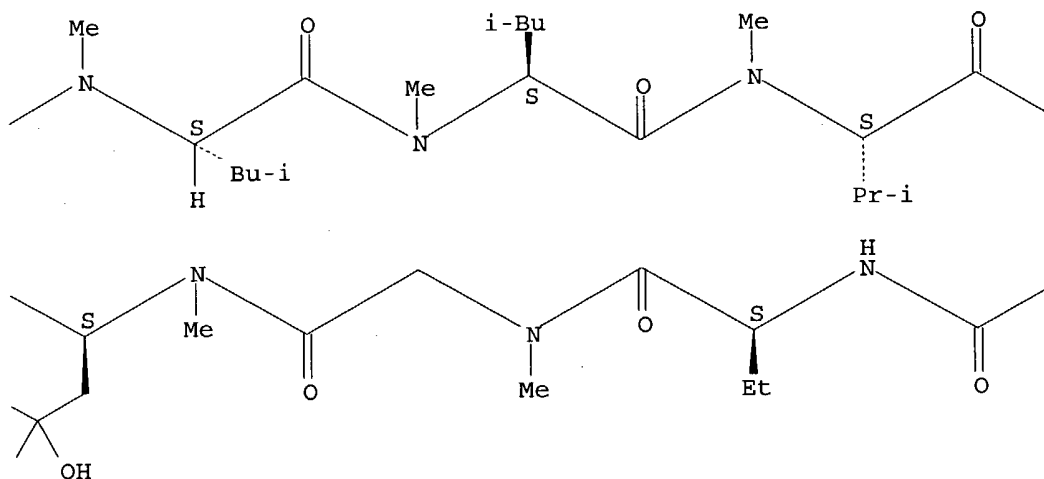
Absolute stereochemistry.

Double bond geometry as shown.

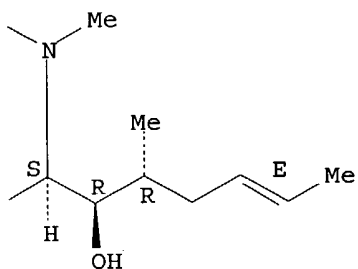
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PAGE 1-B



PAGE 1-C



L66 ANSWER 13 OF 16 USPATFULL on STN
 AN 1999:137216 USPATFULL
 TI Cyclosporin derivatives, their preparation and the pharmaceutical compositions which contain them
 IN Evers, Michel, La Queue en Brie, France
 Mignani, Serge, Chatenay-Malabry, France
 Carry, Jean-Christophe, Meudon, France
 Filoche, Bruno, Creteil, France
 Bashiardes, Georges, Thiais, France
 Bensoussan, Claude, Chevilly-Larue, France
 Gueguen, Jean-Christophe, Chatenay-Malabry, France
 Barriere, Jean-Claude, Bures sur Yvette, France
 PA Rhone-Poulenc Rorer S.A., Antony Cedex, France (non-U.S. corporation)
 PI US 5977067 19991102
 AI US 1998-69959 19980430 (9)
 PRAI FR 1997-5351 19970430
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Tsang, Cecilia J.
 LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
 CLMN Number of Claims: 17
 ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1987

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cyclosporin derivatives of formula (I) in which R is H or a radical (Ia) or (Ib) as defined herein; R' is a radical (Ic) or (Id) as defined herein; and R'' represents H or OH, with the proviso that R and R'' are not simultaneously H, and pharmaceutically acceptable salts thereof, when they exist, are disclosed as useful for the treatment and/or prophylaxis of retrovirus infections. ##STR1##

IT 6006-58-2 7226-23-5 107335-26-2 137718-41-3 138957-22-9
(preparation of novel cyclosporin derivs. and pharmaceutical compns.)

IT 107335-26-2
(preparation of novel cyclosporin derivs. and pharmaceutical compns.)

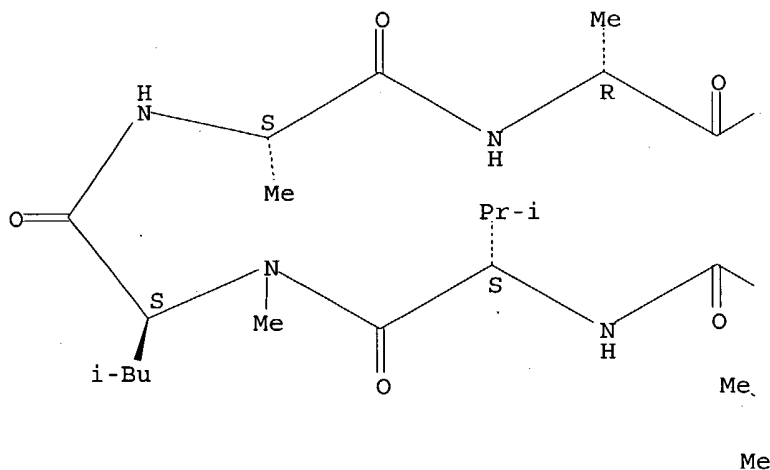
RN 107335-26-2 USPTAFULL

CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

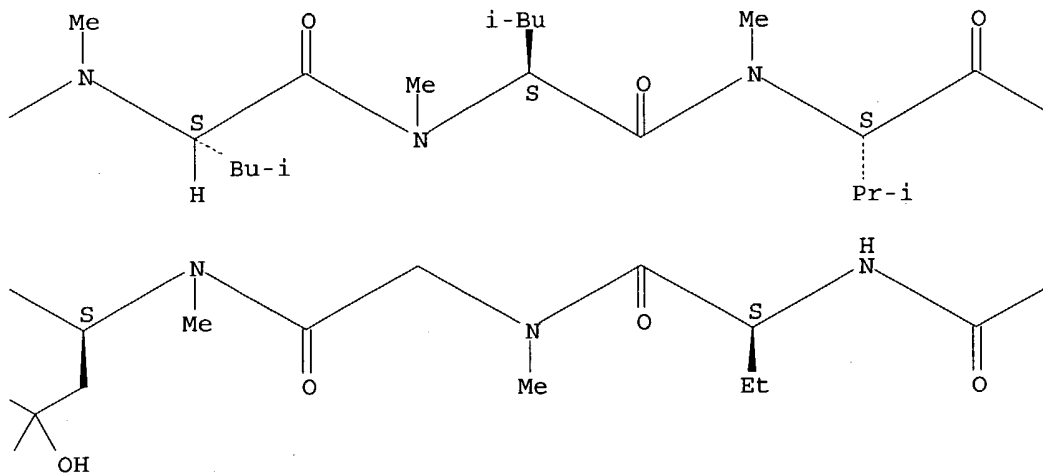
Absolute stereochemistry.

Double bond geometry as shown.

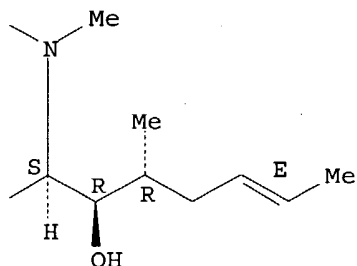
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PAGE 1-B



PAGE 1-C



L66 ANSWER 14 OF 16 USPATFULL on STN

AN 1999:106560 USPATFULL

TI Cyclosporin derivatives with anti-HIV effect

IN Luchinger, Jean Martin, Basel, Switzerland

PA C-Chem AG, Switzerland (non-U.S. corporation)

PI US 5948884 19990907

WO 9704005 19970206

AI US 1997-981597 19971231 (8)

WO 1996-EP3129 19960717

19971231 PCT 371 date

19971231 PCT 102(e) date

PRAI EP 1995-111162 19950717

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner:
Delacroix-Muirheid, C.

LREP Wenderoth, Lind & Ponack, L.L.P.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 460

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns new cyclic peptides of general formula (I)
##STR1## in which the letters A to K signify residues of the following
amino acids: A is substituted homothreonine of the general formula (II):

$$\text{R.sub.1} \text{ --CH.sub.2 CH(CH.sub.3) --CH(OH) --CH(NHCH.sub.3) --COOH}$$

in which R.sub.1 is n-propyl or propenyl in which the double bond is preferably in the trans configuration; B is α -aminobutyric acid, valine, norvaline or threonine; C is a D-amino acid of the general formula (III):

$$\text{CH.sub.3 NH--CH(R) --COOH}$$

in which R is straight-chain or branched-chain C.sub.2 -C.sub.6 alkyl, alkenyl or alkynyl, whereby these groups may be substituted by hydroxy, amino, C.sub.1 -C.sub.4 alkylamino, C.sub.1 -C.sub.4 dialkylamino, alkoxy or acyloxy, COOR.sub.2 or CONHR.sub.2 in which R.sub.2 is straight-chain or branched-chain C.sub.1 -C.sub.4 alkyl X--R.sub.3 in which X is O or S and R.sub.3 is straight-chain or branched-chain C.sub.1 -C.sub.4 alkyl, alkenyl or alkynyl and, when X is S, R.sub.3 may also be aryl or heteroaryl, halogen, preferably fluorine, cyano, CHR.sub.4 R.sub.5 in which R.sub.4 is hydrogen, methyl, ethyl or phenyl

and R.sub.5 is hydrogen, hydroxy, halogen (preferably fluorine), amino, C.sub.1 -C.sub.4 alkylamino, C.sub.1 -C.sub.4 dialkylamino, acyloxy (preferably acetyloxy), tert-butoxycarbonylamino-ethoxy-ethoxy-acetyloxy or alkoxy carbonyl (preferably butoxycarbonyl); D is N-methyl-gamma-hydroxyleucine or N-methyl-gamma-acetyloxyleucine; E is valine; F, I and J are each N-methylleucine; G is alanine; H is D-alanine or D-serine; and K is N-methylvaline. The invention also concerns the preparation of such peptides and their use in the prevention of infection by the human immunodeficiency virus (HIV).

SUMM The present invention relates to novel cyclic peptides from the **cyclosporin** series which have a strong inhibitory effect on human immunodeficiency virus (HIV) without having any immunosuppressive activity. Such cyclic peptides. . . claimed, inter alia, in EP 484 281. One of the substances which is specifically claimed in this patent specification is (gamma-hydroxy-N-methylleucine)**cyclosporin**. While this substance can very readily be prepared from **cyclosporin A** by means of microbial hydroxylation, EP 484 281 indicates that this substance has an activity against HIV which is some 5-6 times weaker than that of the most strongly active substances, namely MeIle-4-**cyclosporin** or MeVal-4-**cyclosporin**. All 3 substances have practically no immunosuppressive activity. Unexpectedly, it has been found that the anti-HIV effect of (gamma-hydroxy-MeLeu-4)**cyclosporin** can be substantially improved, without giving rise to any immunosuppressive activities, by introducing suitable substituents into the methylene group of the amino acid sarcosine in position 3 of said **cyclosporin**. Since the therapeutic doses of **cyclosporin A** which are used after organ transplants in order to prevent rejection of the transplanted organs are very high, and similarly high doses are to be expected for an anti-HIV therapy which uses **cyclosporin** derivatives, the value of the present invention is that it provides novel **cyclosporin** derivatives which possess high anti-HIV activity and that these **cyclosporin** derivatives can be prepared simultaneously, in a few steps, from **cyclosporin A**, which is a product which is already being prepared by the ton.

SUMM . . . of the bases employed, and a broad range of electrophiles, were investigated in detail by Seebach for the case where **cyclosporin A** is the starting compound, are described in the literature (D. Seebach et al., Helv. Chim. Acta, Vol. 76, 1564-1590, 1993),. . . acid C has the (D) configuration. It was demonstrated in the present invention that this is also the case when 4-(gamma-hydroxy)-N-methyl-leucine**cyclosporin** is used as the starting compound instead of **cyclosporin A**. The use of 4-(gamma-hydroxy)-N-methylleucine**cyclosporin** as the starting compound for such transformations is novel and part of the subject-matter of the. . .

SUMM . . . described in Eur. J. Immunol. 1987, 17, 1359. The importance of this transformation is essentially that the immunosuppressive effect of **cyclosporin** is almost completely eliminated in one step.

IT 107335-26-2

(preparation of cyclosporin derivs. with anti-HIV effect)

IT 107335-26-2

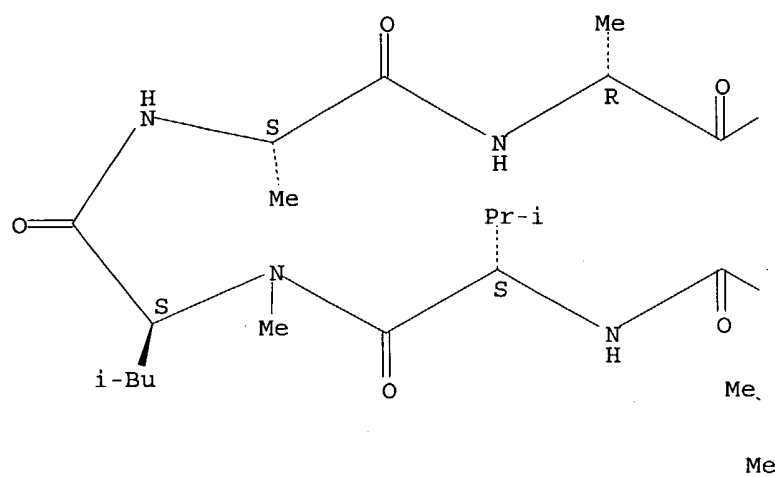
(preparation of cyclosporin derivs. with anti-HIV effect)

RN 107335-26-2 USPATFULL

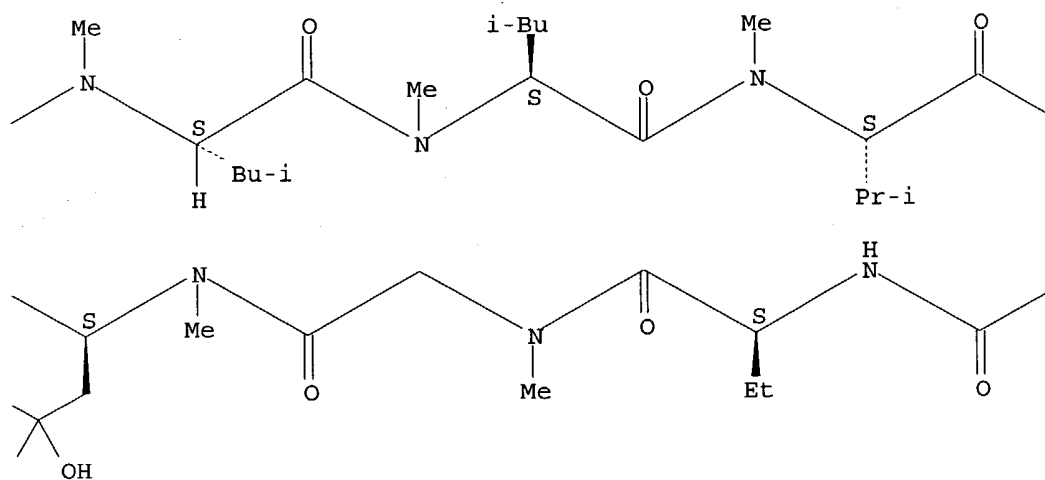
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

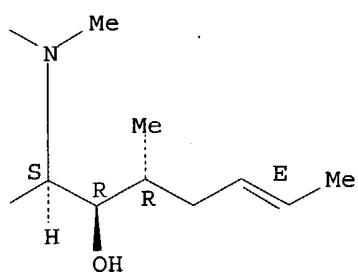
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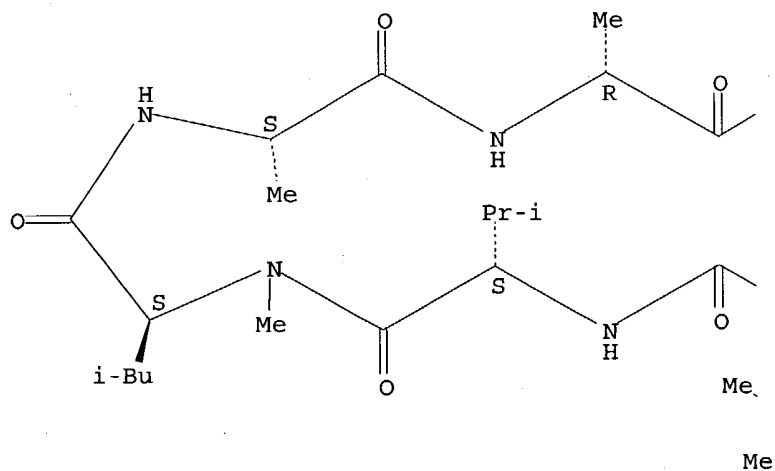
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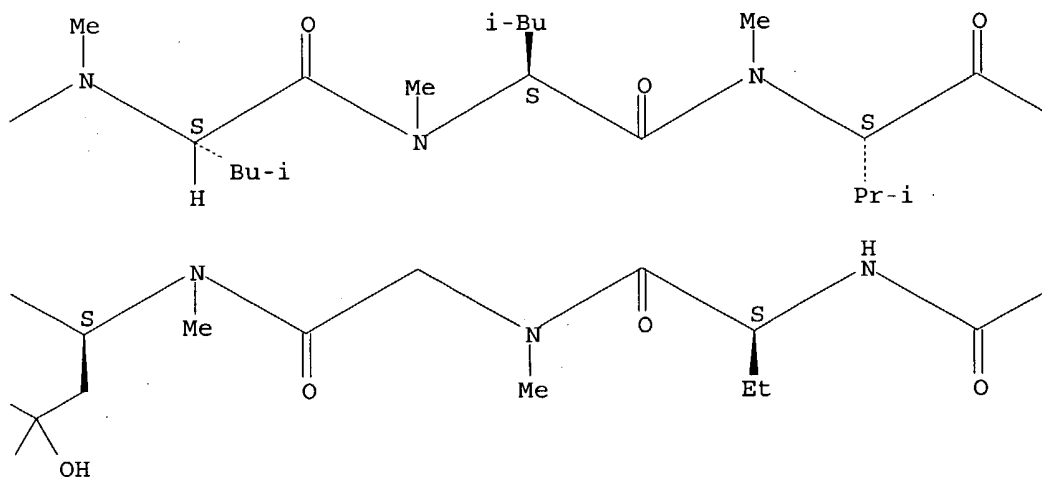
L66 ANSWER 15 OF 16 USPATFULL on STN
 AN 1999:106431 USPATFULL
 TI Cyclosporin compound, its preparation and the pharmaceutical compositions which contain it
 IN Barriere, Jean-Claude, Bures Sur Yvette, France
 Bashiardes, Georges, Thiais, France
 Carry, Jean-Christophe, Meudon, France
 Evers, Michel, La Queue En Brie, France
 Filoche, Bruno, Creteil, France
 Mignani, Serge, Chatenay-Malabry, France
 PA Rhone-Poulenc Rorer S.A., France (non-U.S. corporation)
 PI US 5948755 19990907
 AI US 1997-997613 19971223 (8)
 PRAI FR 1996-15954 19961224
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Tsang, Cecilia J.
 LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
 CLMN Number of Claims: 6
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 290
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The cyclosporin compound of formula (I) is particularly useful in the treatment and/or prophylaxis of retrovirus infections. ##STR1##
 IT 624-92-0, Dimethyl disulfide 107335-26-2
 (preparation of cyclosporin derivs. and their pharmaceutical compns.)
 IT 107335-26-2
 (preparation of cyclosporin derivs. and their pharmaceutical compns.)
 RN 107335-26-2 USPATFULL
 CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

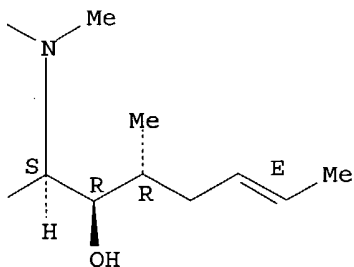
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PAGE 1-B



PAGE 1-C



L66 ANSWER 16 OF 16 USPATFULL on STN

AN 1998:68992 USPATFULL

TI Cyclosporins

IN Ko, Soo Young, London, Great Britain

Kobel, Hans, Basel, Switzerland

Besemer-Rosenwirth, Brigitte, Modling, Austria

Seebach, Dieter, Zurich, Switzerland

Traber, Rene P., Basel, Switzerland

Wenger, Roland, Riehen, Switzerland

Bollinger, Pietro, Bottmingen, Switzerland

PA Novartis AG, Basel, Switzerland (non-U.S. corporation)

PI US 5767069 19980616

AI US 1995-427312 19950424 (8)

RLI Continuation of Ser. No. US 1994-232795, filed on 25 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-57067, filed on 3 May 1993, now abandoned which is a continuation of Ser. No. US 1991-785959, filed on 31 Oct 1991, now abandoned

PRAI GB 1990-23859 19901102

GB 1990-23970 19901105

GB 1990-23971 19901105

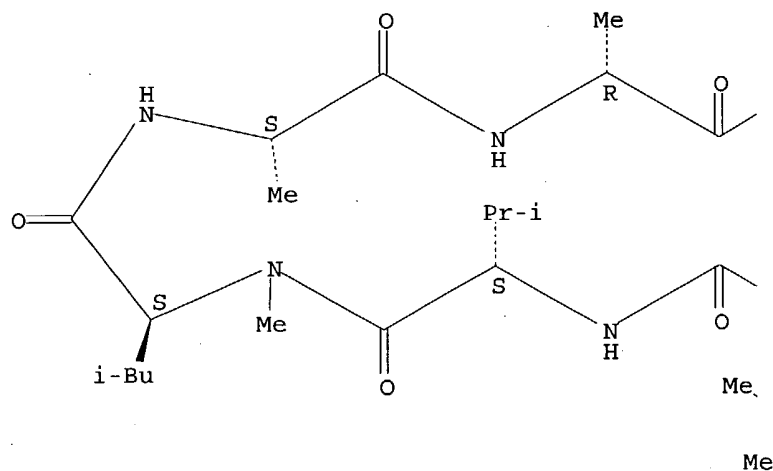
GB 1990-23972 19901105

GB 1991-16836 19910805

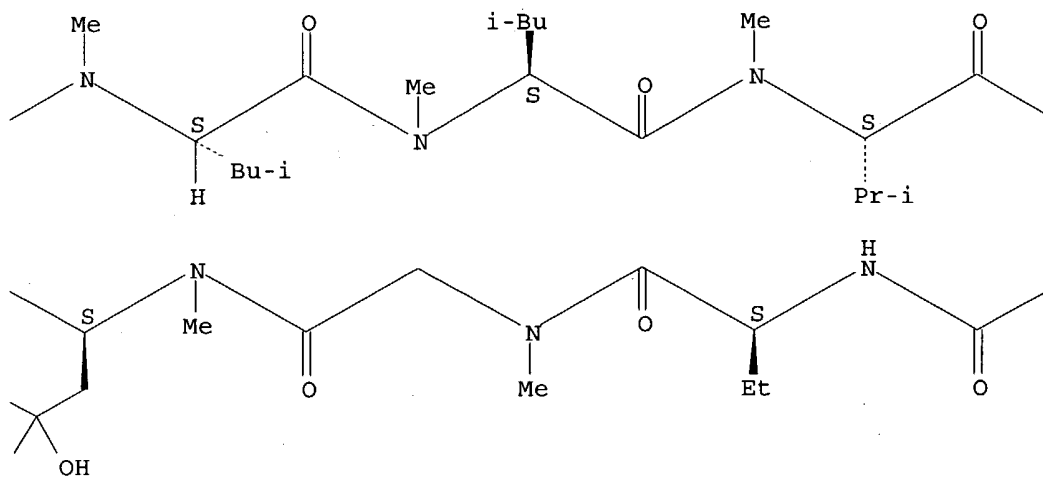
DT Utility
 FS Granted
 EXNAM Primary Examiner: Achutamurthy, Ponnathapura; Assistant Examiner:
 Wessendorf, T. D.
 LREP Mathias, Marla J., McGovern, Thomas O.
 CLMN Number of Claims: 6
 ECL Exemplary Claim: 1
 DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
 LN.CNT 779
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Nonimmunosuppressant cyclosporin derivatives having cyclophilin-binding
 activity, for example, the compound, [MeIle].sup.4 -ciclosporin, are
 useful in inhibiting HIV-1 replication in treating AIDS and AIDS related
 disorders.
 IT 59865-13-3P, Cyclosporin A 79217-60-0P, Cyclosporin 89270-25-7P
 89270-28-0P 107335-26-2P 143205-41-8P 143205-43-0P
 143205-44-1P 143205-45-2P 143222-39-3P 143222-40-6P
 (preparation of, as HIV inhibitor, AIDS treatment in relation to)
 IT 107335-26-2P
 (preparation of, as HIV inhibitor, AIDS treatment in relation to)
 RN 107335-26-2 USPATFULL
 CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

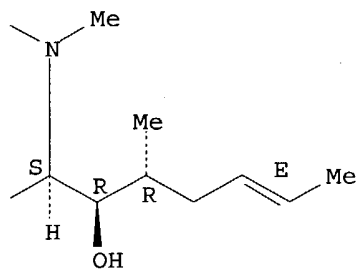
PAGE 1-A



PAGE 1-B



PAGE 1-C



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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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STRUCTURE FILE UPDATES: 11 APR 2004 HIGHEST RN 673857-36-8

DICTIONARY FILE UPDATES: 11 APR 2004 HIGHEST RN 673857-36-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

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L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 89270-25-7 REGISTRY

CN Cyclosporin A, 3-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.

OTHER NAMES:

CN 5: PN: US6686454 SEQID: 5 claimed protein

CN AM 9

CN AM 9 (peptide)

CN Cyclosporin A metabolite 1

CN OL 1

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	location			description
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uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

PATENT ANNOTATIONS (PNTE):

Sequence | Patent

Source | Reference

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Not Given | US6686454

| claimed

| SEQID 5

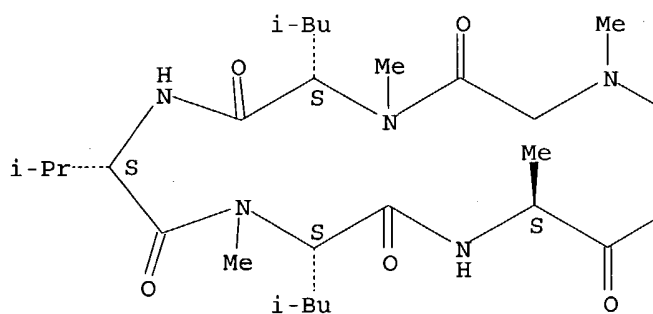
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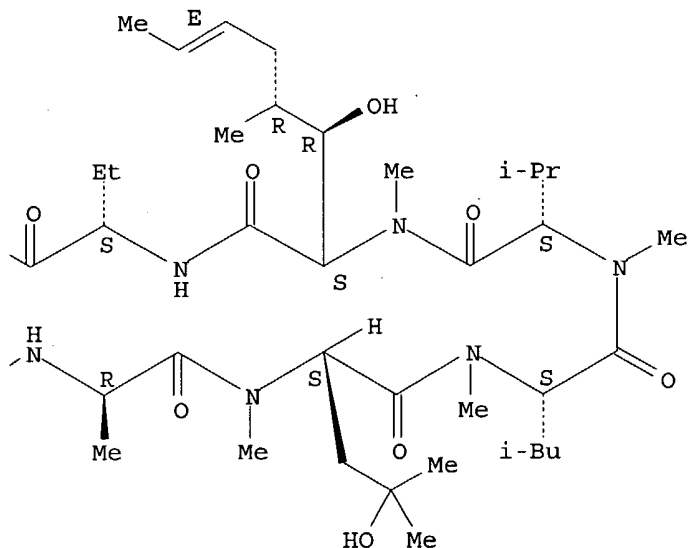
DR 121635-62-9
MF C62 H111 N11 O13
LC STN Files: CA, CAPLUS, IPA, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



110 REFERENCES IN FILE CA (1907 TO DATE)
110 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:192027

REFERENCE 2: 140:144715

REFERENCE 3: 140:104463

REFERENCE 4: 138:348304

REFERENCE 5: 138:348262
REFERENCE 6: 137:319932
REFERENCE 7: 137:179921
REFERENCE 8: 135:86519
REFERENCE 9: 134:305089
REFERENCE 10: 133:290630

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E E13+ALL
L10 2313 S E6+NT
E E9+ALL
E E14+ALL
L11 736 S E6+NT
E E8+ALL
E E15+ALL
L12 20122 S E2+NT
E E8+ALL
E E16+ALL
L13 228 S E5,E4+NT
E E7+ALL
E E17+ALL
L14 428 S E4,E3+NT
E E11+ALL
E E18+ALL
L15 860 S E4+NT
L16 1 S L6 AND L9-L15
L17 1 S L6 AND COSMETIC#/SC,SX,CW,BI
L18 1 S L8,L16,L17

FILE 'REGISTRY' ENTERED AT 07:50:17 ON 13 APR 2004
L19 4 S L3 NOT L5
SEL RN 3 4
L20 2 S E1-E2

FILE 'USPATFULL, USPAT2' ENTERED AT 07:53:00 ON 13 APR 2004

L21 8 S L5
L22 1 S L21 AND HAIR?/BI,CT

FILE 'REGISTRY' ENTERED AT 07:53:24 ON 13 APR 2004

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 07:53:41 ON 13 APR 2004

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FILE COVERS 1907 - 13 Apr 2004 VOL 140 ISS 16
FILE LAST UPDATED: 12 Apr 2004 (20040412/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l18 all hitstr

L18 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:637493 HCAPLUS
DN 137:179921
ED Entered STN: 23 Aug 2002
TI Use of [γ -hydroxy-N-methyl-L-leucine9]cyclosporin A for hair growth
IN Kim, Sang-nyun; Ahn, Ho-jeong; Lee, Chang-woo; Kim, Jung-hun; Kim, Jong-il; Lee, Heon-sik; Lee, Min-ho; Cho, Ho-song; Kim, Seung-jin; Park, Hong-soon
PA Lg Household & Health Care Ltd., S. Korea
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K007-06
CC 1-12 (Pharmacology)
Section cross-reference(s): 16, 62, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064106	A1	20020822	WO 2002-KR141	20020131
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1361850	A1	20031119	EP 2002-712478	20020131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2002165133 A1 20021107 US 2002-73021 20020212
 PRAI KR 2001-7263 A 20010214
 WO 2002-KR141 W 20020131

- AB The present invention discloses a hair growth promoter comprising [γ -hydroxy-N-methyl-L-leucine9] cyclosporin A, in which a hydroxy group is added to a γ carbon of N-methyl-L-leucine at Number 9 position in cyclosporin A by metabolic action of a microorganism, as an active ingredient. This cyclosporin A metabolite was prepared by fermentation with Pseudonocardia autotrophica. The metabolite showed hair regrowth effect comparable to that of cyclosporin A and had lower immunosuppressive effect than cyclosporin A. Hair revitalizing tonic, cream, shampoo, and conditioner formulations are given.
- ST hydroxymethylleucine cyclosporin A hair growth promoter; cyclosporin A metabolite hair prepn growth stimulant
- IT Alcohols, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (C16-18; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (conditioners; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (creams; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (emulsions; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (gels; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (growth stimulants; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (liqs.; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (pastes; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Immunosuppression
 (reduction of side effect of; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Hair preparations
 (sprays; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Drug delivery systems
 (topical; use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Fermentation
 Microsome
 Perfumes
 Pseudonocardia autotrophica
 Shampoos
 (use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT Paraffin oils
 Petrolatum
 Polyoxyalkylenes, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)
- IT 59865-13-3, Cyclosporin A

RL: BCP (Biochemical process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

IT 89270-25-7P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

IT 89270-23-5P, Cyclosporin A metabolite 21 89270-28-0P, Cyclosporin A metabolite 17

RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

IT 156047-45-9

RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

IT 13139-15-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

IT 56-81-5, Glycerin, biological studies 57-55-6, Propylene glycol, biological studies 58-95-7, Tocopherol acetate 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 94-13-3, Propylparaben 99-76-3 111-02-4, Squalene 122-19-0, Stearyltrimethyl benzylammonium chloride 544-31-0 2216-51-5 9004-82-4 9005-64-5, Tween 20 25265-71-8, Dipropyleneglycol 25322-68-3, Polyethyleneglycol 31566-31-1, Glycerine-monostearate 32128-65-7, Polyoxyethylene octyldodecylether

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Novartis Ag; US 5807820 A 1998 HCAPLUS

(2) Sandoz Ltd; EP 414632 A 1989 HCAPLUS

IT 89270-25-7P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(use of [γ -hydroxy-N-Me-L-leucine9]cyclosporin A for hair growth)

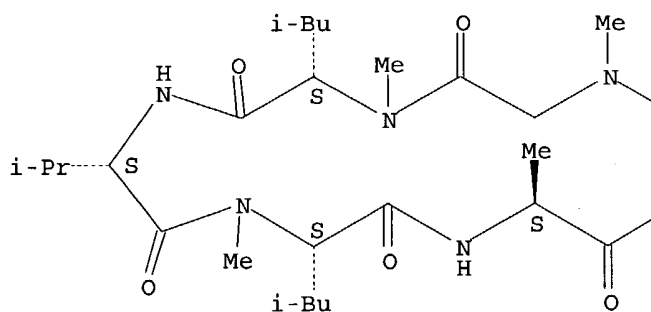
RN 89270-25-7 HCAPLUS

CN Cyclosporin A, 3-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

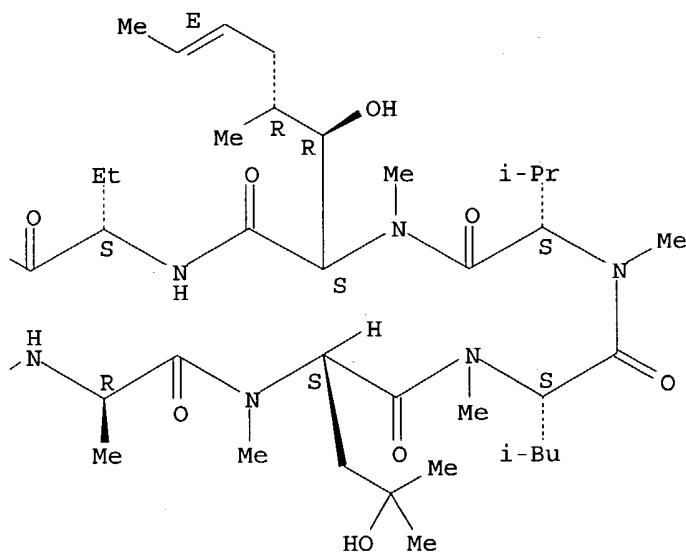
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



=> fil uspatall

FILE 'USPATFULL' ENTERED AT 07:53:49 ON 13 APR 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 07:53:49 ON 13 APR 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d bib abs hitstr l22

L22 ANSWER 1 OF 1 USPATFULL on STN

AN 2002:295088 USPATFULL

TI Use of [gamma-hydroxy-N-methyl-leucine9] cyclosporin a for hair growth

IN Kim, Sang-Nyun, Yusong-gu, KOREA, REPUBLIC OF

Ahn, Ho-Jeong, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Chang-Woo, Seo-gu, KOREA, REPUBLIC OF
 Kim, Jung-Hun, Yusong-gu, KOREA, REPUBLIC OF
 Kim, Jong-Il, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Heon-Sik, Yusong-gu, KOREA, REPUBLIC OF
 Lee, Min-Ho, Yusong-gu, KOREA, REPUBLIC OF
 Cho, Ho-Song, Seo-gu, KOREA, REPUBLIC OF
 Kim, Seung-Jin, Yusong-gu, KOREA, REPUBLIC OF
 Park, Hong-Soon, Yusong-gu, KOREA, REPUBLIC OF

same application

PI US 2002165133 A1 20021107
 AI US 2002-73021 A1 20020212 (10)
 PRAI KR 2001-7263 20010214
 DT Utility
 FS APPLICATION
 LREP VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP, P.O. BOX 34385, WASHINGTON,
 DC, 20043-9998
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN 5 Drawing Page(s)
 LN.CNT 577

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses a **hair** growth promoter comprising [γ -hydroxy-N-methyl-L-leucine^{sup.9}] cyclosporin A, in which a hydroxy group is added to a γ carbon of N-methyl-L-leucine at Number 9 position in cyclosporin A by metabolic action of a microorganism, as an active ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **89270-25-7P**

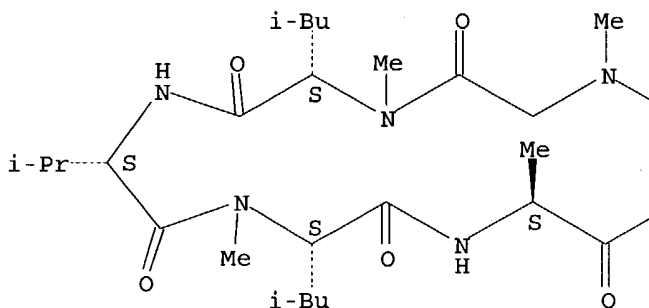
(use of [γ -hydroxy-N-Me-L-leucine⁹]cyclosporin A for hair growth)

RN 89270-25-7 USPTFULL

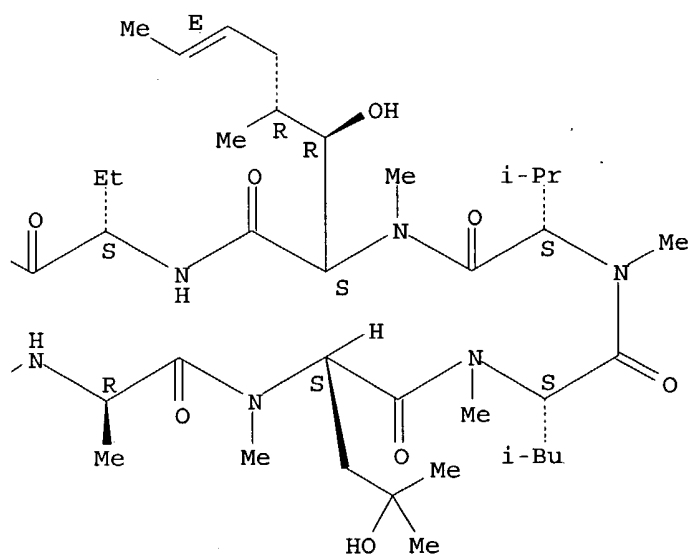
CN Cyclosporin A, 3-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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